The New England
Journal of Medicine

Copyright, 1944, by the Massachusetts Medical Society

Volume 231 DECEMBER 7, 1944 Number 23

THE STUDY OF THE PATIENT FROM A PSYCHOSOMATIC STANDPOINT*

KENNETH J. TILLOTSON, M.D.†

BELMONT, MASSACHUSETTS

AMONG the most recent advances in medicine resulting directly from the present war are the employment of the sulfonamides and penicillin to combat infection and that of blood plasma to combat shock. Both depend on their prompt use after injury, and delay may result in loss of the therapeutic opportunity. A third and comparable medical contribution may be added — the early recognition of psychoneurotic or emotional symptoms and their prompt treatment and management. Failure to recognize the nature of these emotional manifestations may mean delay in promptly and effectively treating the patient. Psychoneurotic disorders manifest themselves in the following manner: pain, headaches, nervousness, indigestion, dizziness, weakness, backaches and a host of other somatic complaints. These physical signs of emotional maladjustment are termed "psychosomatic symptoms." First aid in the form of prompt psychiatric treatment has already become as valuable to the armed forces and to the people of civilian areas under bombardment as have the quick recognition of a physical injury and the knowledge of how and where to apply a tourniquet to control bleeding.

There is a close parallel between first aid for physical casualties and that for so-called "mental casualties," also known as emotional maladjustments or nervous conditions, or, perhaps more correctly, psychoneuroses or psychosomatic reactions. The immediate treatment of these complaints — often severe or hysterical in character, and at times even constituting excited or psychotic reactions — forms a valuable therapeutic contribution, since a large percentage of patients with these previously disabling disorders are now completely cured, and considerable numbers of men in the armed forces are even returned promptly to active combat duties.

This method of treatment is called "narcosynthesis," and consists of administering Pentothal Sodium intravenously until a certain stage of narcosis is reached. When in this state, the patient reexperiences the intense emotions that were originally associated with the traumatic battle experiences and that have been perpetuated in various stages of repression up to the moment of treatment. He actually synthesizes the emotions and memories connected with the experience. Under the influence of the drug the physician uses psychotherapy to free the patient of the intense repressed emotions that cause the neurotic symptoms, and the latter emerges from the narcosis with relief from his abnormal reactions and with new emotional drives, and returns in a state of renewed strength to a world of reality, both past and present. In certain cases in which the narcosynthesis does not produce the desired result, electric shocks may be given. Both the foregoing procedures depend on marked physiologic changes produced either chemically or electrically, as well as psychotherapy, to reverse the psychologic state of the patient. These newer methods and procedures have already altered the nature of present-day psychiatric practice, and it is probable that further and equally revolutionary changes will follow with the increasing demand for psychiatric treatment resulting directly or indirectly from the present war.

Prior to World War I, neuropsychiatric disorders were treated most unsatisfactorily and by a comparatively small group of psychiatrists and neurologists, most of whom were attached to mental hospitals. Such complaints and symptoms could not be dealt with in the forthright manner in which most medical symptoms were approached, for popular sentiment — including the attitude of the medical profession — toward nervous and mental diseases was extremely unscientific and at best depicted little understanding. In World War I, however, under the spur of necessity, there was revealed not only the frequency with which neuropsychiatric complaints occur but the high percentage of psychoses and psychoneuroses existing in the civilian population. Attention was also drawn to the psychosomatic elements that affect a large number of persons who, to be sure, are suffering from medical or surgical conditions, but whose treatment and management are severely complicated by emotional or psychoneurotic factors. There was thus introduced an entirely new field of thought, and in this

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 23, 1944.

†Instructor in psychiatry, Harvard Medical School; psychiatrist-in-chief, McLean Hospital.

way there began the development of present-day psychosomatic studies that are applicable not only to neuropsychiatric patients but to all patients.

Twenty years ago, when many of those now in practice were medical students, psychiatry and the study of nervous disorders presented problems that seemed not only mysterious but infinitely complex. From the available literature and from the meager instruction current in medical schools at that time, it was difficult to obtain a concise and unbiased presentation of the mechanisms that underlie abnormal behavior and emotional disorders.

The professional vernacular presumed an acquaintance with much, although it was not a part of ordinary experience, and in lieu of actual experience with neuropsychiatric disorders as then understood, a few stereotyped descriptions of the vintage of Janet, Charcot, Babinski and Kraepelin served to give an understanding of neurologic and psychiatric disorders, together with equally unsatisfactory descriptions of the end stages of manic-depressive psychoses and dementia praecox. The medical profession as a whole had not as yet discovered the importance of the dynamic and emotional factors in psychologic medicine, nor did it realize that the psychologic components — namely, the emotional factors and neuropsychiatric disorders as such — were frequently not considered or missed in diagnosis. This state of things resulted in much unnecessary chronic illness, to say nothing of an immense amount of needless surgery.

The psychogenic hypothesis was first outlined by Brodie as long ago as 1837. It stressed the importance of the unconscious to the development of personality and to subsequent emotional experience — a subject that was later presented and elaborated by Freud, Jung and others. Generally speaking, twenty years ago little was known about psychodynamics, psychopathology and psychobiology; all of which means that nothing was known, practically speaking, of the tremendous field of the unconscious and its relation to the causes of psychoneuroses, the importance of psychosomatic relations and the early emotional manifestations and symptoms of all disease or illness.

In World War I, psychiatry began to be recognized as having an important contribution to make. For the first time it was given, although reluctantly, a place of slight responsibility along with the other medical specialties. With the development of postwar psychiatric problems in returning veterans, neuropsychiatric disorders began to be placed on a responsible medical footing. It remained for a better understanding of psychosomatic medicine and its integration with the daily practice of general hospital medicine to demonstrate its value. From the application of physiologic principles, together with a psychologic understanding of the patient, successful treatment of psychoneurotic disorders became an accomplished fact, and the field of neuropsychiatry could be said to stand on a firm scientific basis and from a clinical standpoint to compare favorably with other specialties.

How does this relate to the problems of mental health in the present armed forces and the mental health of the civilian population under the stress of the present war? It is frequently asked what the psychologic effects of war are on civilians and military personnel, whether the war has developed any new types of nervous and mental disorders, and whether present-day neuropsychiatrists and the medical profession in this country are adequately equipped to handle such conditions. The final answer rests on the ability of the medical profession to practice psychosomatic medicine and to face intelligently the ever-increasing emotional factors and their influence on personality as well as on the patient's physiologic state.

The psychologic effect of war on civilians and soldiers and sailors may be disastrous in that predisposed tendencies may become activated and emotional symptoms, a neurosis, a psychoneurosis or even an actual psychosis may develop. That these disorders are no different from the prevailing disorders of the last war, psychiatrists seem to agree. The so-called "shell shock" of World War I might be anything from a neurosis to a psychosis of the most profound character. The exhaustion or fatigue syndromes of the present war and the psychosomatic complaints are again a mere repetition of psychoneurotic complaints, varying in manifestation, intensity and duration and also in response to treatment, depending largely on the constitutional factors in the given patient. That there are not enough psychiatrists at the present time to deal with the vast number of neuropsychiatric casualties in the armed forces is evidenced from all quarters. For instance, some time ago a bulletin from the War Department stated that any medical officer might be called on to treat neuropsychiatric casualties because of the shortage of psychiatrists. The burden of treating these casualties will fall on medical officers without specialized training. This fact may be more vividly portrayed by the following figures. An average of 8 to 20 per cent of the men examined for military service are rejected for psychiatric reasons, and 40 per cent of the discharges from the armed forces are made for psychiatric reasons. In contrast, about 2 per cent of the members of the medical profession are neuropsychiatrists. In addition, one third of the neuropsychiatrists in this country are now in the armed forces. The social implication of these figures is enormous, but their importance to the medical profession and to the general practitioner is even greater and more challenging. Every physician is aware of the fact that even in peacetime 40 to 60 per cent of the patients seeking medical help present essentially emotional problems or frank psychiatric disorders. A major result of the war experience is the compelling necessity to focus at-

tention on a large section of the population who need medical care and who previously may not have recognized this need. No doubt there will also be a considerable increase in the number of patients with disabling functional illnesses seeking help from every specialty of the medical profession.

The most frequent diagnosis of these disabilities by far is that of psychoneurosis — a term that connotes a great number of clinical entities. Unfortunately, ordinary neuropsychiatric disorders have been thought to occur only in those with personality defects or, generally speaking, in weaklings. This is not true. A fair proportion of neuropsychiatric patients give no history of previous difficulties. Under the extremes of fatigue and the stress of modern combat, the most stable person may reach his breaking point. Thus the presence of neuropsychiatric disorders in combat must be looked for in the normal persons as well as those predisposed to such abnormal states.

In soldiers, the factors that precipitate emotional disorders with resulting psychosomatic symptoms include separation from home, regimentation, lack of freedom, lack of privacy, lack of feminine companionship, a feeling of not being appreciated and a lack of confidence in leaders. In combat, there are extreme fatigue, danger and long exposure to death, malnutrition, exposure to heat and cold, disease, isolation, confusion, hunger and the fear of being a coward or of losing one's self-control, as well as the realization of the responsibility for the lives of others, insufficient understanding of war or lack of the conviction to fight.

A distinction may well be made between the treatment and the management of psychoneuroses. Treatment depends on the type of disorder and its duration, the ability of the physician and the degree of rapport that is developed between him and the patient. Obviously a great many patients are treated without being cured. Probably few psychoneurotic subjects are treated by competent physicians without being relieved. The result obviously depends not only on the method of treatment and the ability of the therapist, but on the type of patient and the nature of the psychoneurosis.

If the study of psychosomatic factors and the approach to the patient are correct, the only rational method of treatment consists in the revealing to him of the unconscious mental processes that are responsible for the symptoms or illness as a whole, by bringing into consciousness the repressed impulses that find vicarious satisfaction in symptoms. The patient must be given an insight into why he has symptoms and how they are produced and what they mean at the psychologic or psychobiologic level, and must be shown that nervousness and emotional tension result from conflicts and frustrations. In some cases this is relatively easy. In many others, however, it is extremely difficult, because therein lies the crux of the problem. Many psychoneurotic patients are highly intelligent and see the surface problem together with its ramifications and implications, yet are utterly at a loss to resolve it.

A psychoneurosis is not a matter of logic, and no amount of intellectualization will cure a state that is emotionally so deeply conditioned. Adjustment is not always or even generally possible, not alone because many of the inner emotionally toned conflicts are difficult to discover and resolve, but because most of the social and environmental factors are beyond the control of the therapist and many beyond the ability of the patient to mold to his own needs. If, however, the basic personality patterns cannot be changed, the patient may get relief through appreciation and understanding of the true nature of the illness.

Take, for example, a patient recently under treatment who had a typical neurasthenic type of psychoneurosis. A physician told her that the weakness and low blood pressure were indicative of a pituitary syndrome. He gave her many hormones and endocrine substances and had her remain in bed for months, but finally accomplished a fairly satisfactory shock treatment by telling her one day, "Of course you might as well know you have a serious pituitary disorder, Simmonds's disease, and you will gradually become a completely bedridden invalid." She was naturally quite overwhelmed and finally asked for a consultation. She was sent to a Boston hospital where an internist decided that she did not have the serious pituitary disorder, and ordered her out of bed. He informed her, however, that she did have a nervous disorder and referred her to a psychiatrist. Soon afterward she consulted me. Her co-operation in a reasonably active program, even including housework, which she had been told she would never be able to do, was excellent. More obvious conflicts, such as an incompatible sex relation with her husband occasioned by fear of pregnancy due to a severe and near fatal post-partum hemorrhage following her last childbirth, along with many other emotional problems, have been worked out. The development of a proper and hygienic routine of life and reassurance and definite proof that she can live an active, useful life constitute an improved state, and furnish a good example of the management of a psychoneurotic patient of the neurasthenic type.

Many acute tension and anxiety states must be dealt with on a symptomatic basis while the deeper and more fundamental psychologic factors are being explored. This necessitates management. If employment is cut off, a program of occupational therapy or physiotherapy and exercise must be instituted, unless a period of rest and heavy sedation is indicated. Small doses of drugs or refraining from the use of drugs is the safest policy unless a period of sedation is for some reason believed de-

sirable for the patient's immediate needs. In many cases chemotherapy enhances the value of psychotherapy.

An important point in the management of psychoneuroses is that the patient with psychogenic pain, headaches, insomnia, vomiting, tremors or feelings of tension, and combinations of these, believes that the symptoms are as real as an organic disease. Indeed, most patients insist that they would rather have pneumonia or surgical conditions requiring operation than this so-called "nervousness."

A patient with anxiety hysteria or obsessional states has a real illness, and reassurance may be of little value. He fears insanity, death, cancer, syphilis or some lingering disease. I treated periodically for several years a neurotic patient with the obsession that he had syphilis. Hinton tests and reassurance by a formidable array of outstanding medical consultants only gave him possible loopholes as he played one against the other. After a detailed medical, social and somewhat psychoanalytical approach through periods of free association, and after thorough physical examinations, it was finally discovered that at the age of twelve or fourteen the patient caught his mother in a sexual act with a man whom he later heard had syphilis. The emotional shock of the affair and his strong dislike for the man, together with the fact that his father had divorced the mother several years later because of her infidelity, made him build up a long and varied train of extremely painful conflicts. These revealed themselves in a real neurosis when he married, and his own marital situation suddenly overwhelmed him when he recalled an experience he had had in college with a prostitute while under the influence of alcohol. His long developing doubts and emotional conflicts were first manifested in anxiety; he then became fearful that he had contracted syphilis. When the steps of this development had been shown to the patient, he became much better. In fact, he made a good recovery over a period of two or three years, with several interruptions of otherwise fairly constant therapy.

To be successful, then, treatment must be directed to the individual problems of the patient and should reckon with his special personality profile. Psychotherapy actually begins the moment the patient enters the office, and both a detailed psychologic study and a careful physical examination are directed to that end. The physical examination, in particular, not only is useful for the purpose of excluding organic disease but serves as an excellent therapeutic measure in that it convinces the patient that his complaints are being seriously considered.

Nonne[1] wrote, "The war has shown that persons with a previously sound nervous system can acquire a neurasthenia complex, and hysteria is no rarity in war, even in persons hitherto quite healthy." An illustration of this fact is furnished by the experience of an officer from an American cruiser who had recently returned from the Mediterranean theater. Recounting his experiences in connection with his own neurotic disorders, he told of an experience concerned with the picking up of a transport plane in the Sicilian campaign. When the paratroopers in the plane had been commanded to jump, all had done so except an eighteen-year-old soldier. The officer leveled his revolver at the boy, who said, "Go ahead and shoot — I can't jump." When the paratrooper came aboard the cruiser, he wept hysterically, just as he had been seized with extreme terror and fright, which resulted in a complete numbness and inability to jump, when ordered to bail out, although always before in training he had experienced no trouble. The effect of this situation on the ensign was closely identified with his own anxieties and fears. The ensign wept bitterly and denounced the officer. "That yellow . . . tongue-lashed and threatened the poor kid all the way back to Africa amidst the suffering and groans of a boatload of wounded men." The ensign, who was on active duty, had consulted me believing he should resign from his naval post and return to civilian life to take up the study of medicine, since doctors were so badly needed. He thought that he could return to the front after completing his medical education and really do some good.

The outstanding cause of psychoneuroses, apart from a predisposition under actual service conditions, is undoubtedly fear of death or disablement. The symptoms exist because the patient is afraid, and they persist so long as there is any conflict between a desire for self-preservation and a sense of duty. If he is removed from duty permanently or if he refuses point-blank to face danger again, even to the extent of facing the disciplinary action or consequences that may be in store for him, he loses his symptoms, sometimes in a few hours. Other factors that have been alleged, such as guilt over killing, are infinitely rarer.

The psychosomatic study of the patient should begin with the complaint problem or the presenting symptoms. The underlying personality profile and emotional factors lead to evaluation of the part played by these emotions and anxieties in the development of the bodily symptoms. Queer behavior or conduct disturbances are not alone caused by psychologic or emotional factors. A review of recent publications in the field of psychosomatic medicine reveals that there is practically no physical disease or illness that is not caused or complicated by psychologic factors. This has been repeatedly demonstrated in such ordinary medical conditions as peptic ulcer and anorexia nervosa. The latter has been described as a psychosomatic entity, and in fact practically every medical disease is precisely that.

The psychosomatic approach must therefore take into consideration that the patient is a human

being with worries, fears, hopes and despairs, with the psychologic means of unconsciously converting these emotions into physical symptoms or of otherwise modifying the body physiology. This is most strikingly demonstrated in affective disorders, that is, in depressive states, from reactive depressions to manic states and involutional melancholia. A recent review of the results of electric-shock treatment of the foregoing disorders at the McLean Hospital not only demonstrates outstanding therapeutic results as compared to a control group treated without the aid of electric shocks, but clearly demonstrates the reversibility of the emotional or psychologic symptoms, with simultaneous dramatic changes in the body physiology.[2] The precise nature of these changes is not exactly understood, but the psychosomatic relations have been clearly demonstrated.

It may be of interest to note a few of the results of electric-shock treatment in a series of 70 patients with depressive states, as compared with a control group of patients suffering from the same types of depression but treated without electric shock. Eighty per cent of the treated group showed remission, as against 50 per cent of the control group. The quality and permanence of recovery in the shock group was almost twice as high as in the other group, and the hospitalization of the former group varied from one to two months — 90 per cent less than that in the control group.

* * *

Psychiatrists have utilized the psychosomatic study of patients to a far greater extent since the use of the various shock therapies were introduced about ten years ago. The concept of the study and treatment of the personality as a whole on an individual basis has been one of the most important contributions of psychiatry to general medicine. Since physicians are now being called on to treat and manage an increasing number of psychoneuroses, as well as emotional states manifested by psychosomatic symptoms in a variety of illnesses, these psychosomatic considerations should be more widely accepted, utilized and integrated into the daily practice and experience of the general practitioner.

References

1. Nonne. Cited by Dunbar, H. *Emotions and Bodily Changes: Survey of literature on psychosomatic interrelationships.* 595 pp. New York: Columbia University Press, 1935. P. 374.
2. Tillotson, K. J., and Sulzbach, W. Comparative study and evaluation of electro-shock therapy in depressive states. *Am. J. Psychiat.* (in press).

PILONIDAL CYST

An Analysis of 132 Consecutive Cases

Lieutenant Colonel H. H. Hamilton, M.C., A.U.S., Lieutenant Colonel B. S. Custer, M.C., A.U.S., and Captain A. Kellner, M.C., A.U.S.

THIS study of the problem of pilonidal cyst is based on a review of 132 consecutive cases discharged from a station hospital from July 1, 1942, to October 1, 1943 — a fifteen-month period. At the beginning of the study, a method of preoperative classification and grading of cases was worked out. A policy was set and maintained throughout not to release a patient to duty until healing was complete. Various types of operations have been used during the study of this series of cases. Conclusions were reached after analyzing the first 66 operated cases.

The preoperative classification of cases adopted was as follows:

Grade 1. On examination, the patient presents a sinus or sinuses and a palpable tumor, but there is no history of inflammation, that is, no local pain, swelling or discharge. If the case has been properly graded, the report of the pathologist indicates only fibrosis and giant-cell reaction, with minimal round-cell infiltration.

Grade 2. The patient presents a history of discharge and recurrent local tenderness and swelling, but not within the eight weeks prior to examination. Pathologically, the lesion of this grade of case shows chronic inflammation, as evidenced by a plasma-cell and lymphocytic-cell reaction.

Grade 3. The patient presents a history of recurrent discharge or previous abscess formation requiring drainage, or both. At the time of admission examination reveals local induration and tenderness. Pathologically, the lesions in these cases show acute and chronic inflammation, as evidenced by infiltration with neutrophils, lymphocytes and plasma cells.

Grade 4. At the time of examination the patient presents acute suppuration and abscess formation. Pathologically, there is gross pus and necrotic tissue.

Grade 0 (included for completeness). These cases are frequently referred for attention and are subclinical in type. Examination reveals a sacrococcygeal dimple that is completely epithelialized and contains no tumor mass at the bottom of the dimple. The tip of the coccyx invariably curves posteriorly, a point of great assistance in differential diagnosis. (In reviewing this series of 132 cases a single case of Grade 0 was noted; this was improperly classified as Grade 1 and failed to disclose any cyst on microscopic section.)

In arriving at the proper preoperative grading, white-cell and differential counts were of no benefit. Determinations of the erythrocytic sedimentation rate were also of little value. In borderline cases exhibiting no other evidence of disease within the previous three weeks, the sedimentation rate was of some value in so far as a rate above 10 mm. per hour by the Wintrobe method or above 15 mm. per hour by the Westergren technic, without any complicating disease, indicated that a careful, close study of the specimen should be made before the type of closure was decided on. Studies of frozen sections were carried out in a few cases of this type, but cutting of the cyst is difficult and the procedure is impractical. In order of importance, the results of physical examination, the history and the laboratory findings are the three items used in determining a grade.

This series was preoperatively graded as follows: Grade 1, 45 cases; Grade 2, 24 cases; Grade 3, 45 cases; Grade 4, 9 cases; ungraded, 9 cases. Four of the 9 ungraded cases did not come to operation because of separation from the service for other defects or a history of cysts that had been previously operated on, with breakdowns.

Type of Operation

In evaluating this problem, 128 cases were considered since, as stated above, 4 of the ungraded cases did not come to surgery. The 5 remaining ungraded cases were all treated by excision and packing.

Excision and primary closure. This was done in 43 Grade 1 cases, with 1 failure (2 per cent); in 20 Grade 2 cases, with 2 failures (10 per cent); in 19 Grade 3 cases, with 10 failures (53 per cent); and in none of the Grade 4 cases. Failure is defined as any primary closure that required reopening or that on follow-up examination showed tissue breakdown or evidence of recurrence. The procedure of Ferguson and Mecray[1] (Figs. 1 and 2) was followed, with only minor modifications. With the patient in the Kraske position, and under a low-spinal or local anesthetic, the cyst and overlying skin are excised, strict attention being given to hemostasis. No preliminary injection of dye is used, and sutures of No. 50 black cotton are used on all bleeding points and to close the subcutaneous space. Three or four vertical mattress sutures of No. 30 steel-alloy wire are used to approximate the sacrococcygeal fascia and are tied over dental cotton rolls. Sutures of No. 20 cotton are used to approximate the skin. Postoperatively the patient is encouraged to lie on his back for at least an hour, and if possible, measures are

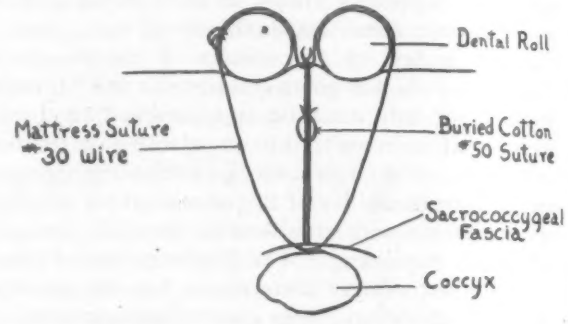

Figure 1. *Schematic Cross Section of Modified Ferguson[1] Operation.*

taken to prevent defecation for five days to a week. The sutures are removed on the tenth postoperative day; the patient becomes ambulatory on the twelfth day and is returned to duty on the eighteenth to twenty-first day. In the 82 cases treated by primary closure, including the failures, the average time from operation to return to duty was twenty-five days.

Excision and packing. In the first 66 cases reviewed in this series 24 (37 per cent) were managed

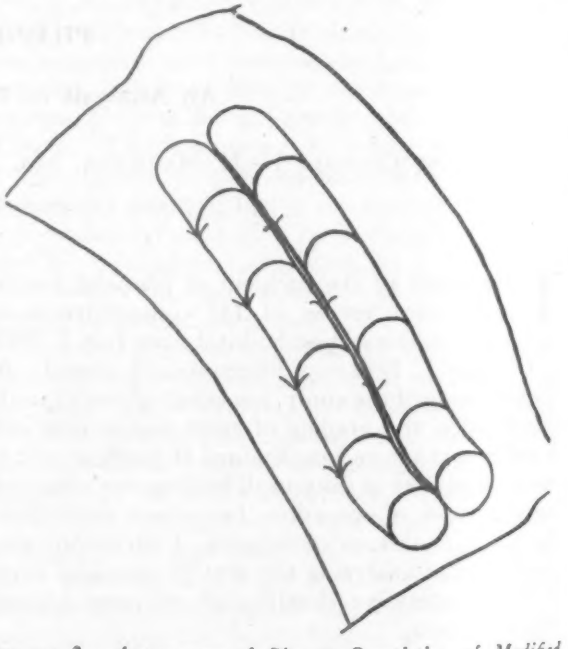

Figure 2. *Appearance of Site at Completion of Modified Ferguson[1] Operation.*

in this manner, and the average time of hospitalization was sixty-two days. Of the remaining 62 cases, only 4 received this type of management and the average period of hospitalization was one hundred and two days. This procedure has been almost entirely supplanted by partial closure.

Partial closure. The technic used in these cases was that of MacFee[2] (Figs. 3, 4, 5 and 6). This type of management was used in 11 of the final group of 62 cases. Nine of these cysts were Grade 3, 1 was

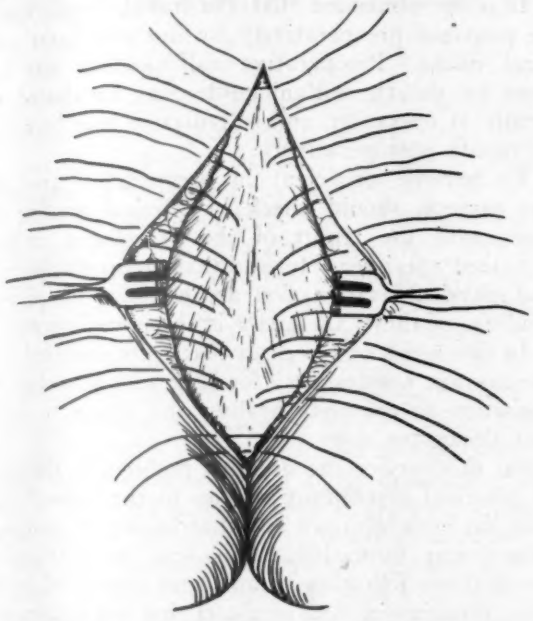

FIGURE 3. *MacFee[2] Type of Partial Closure.*
Mattress sutures of No. 20 cotton have been placed through the skin edges and fascia and are ready for tying.

Grade 4, and 1 was Grade 1, being too large for complete closure. The average time from operation to return to duty in this group was forty-five days.

Incision and drainage. This procedure was limited to 7 cases of gross suppuration and abscess formation.

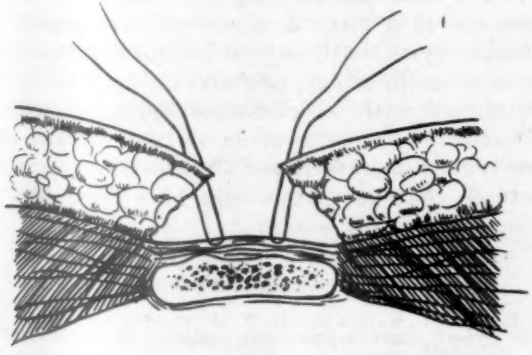

FIGURE 4. *MacFee[2] Type of Partial Closure.*
This represents a cross section of the partial closure.

Nearly all these lesions were quite simple in type. Incision and drainage is done at the outset, and careful use of cauterizing agents effects a cure in simple types of abscess. Care is taken to excise the fistulous tracts at the time of operation, and 3 to 5 gm. of sulfanilamide powder is inserted, followed by loose packing, which is left for a week. After this, Carnoy's solution (absolute alcohol 6 per cent, chloroform 3 per cent, glacial acetic acid 1 per cent and ferric chloride 1 per cent) is applied to the granulating walls with an applicator, left for two minutes and flushed out with saline solution. This is done once daily until a clean, healthy, granulating surface is presented. These patients were discharged to duty as healed on an average of twenty-seven days after operation. Small areas of recurrence are

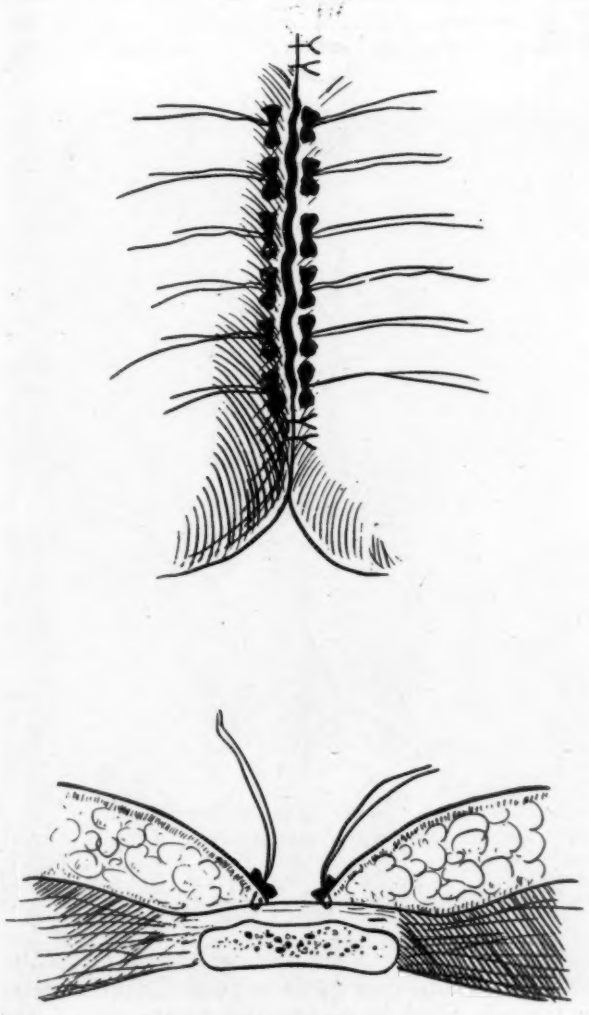

FIGURE 5. *MacFee[2] Type of Partial Closure.*
The sutures are tied over small pieces of rubber dam, bringing the skin edges to the fascia without tension.
In the lower sketch, showing a cross section, note that the sutures are left long.

apt to appear in this type of case, but none has been observed in this group, some of which have been followed for more than a year.

COMMENT

Grade 1 and Grade 2 cases have been satisfactorily closed by a modified Ferguson technic. Sixty-three cases were managed in this manner with 3 known failures. After discharge to duty, all these

patients have been re-examined at monthly intervals as long as they have remained on this field, and the follow-up study has been efficient enough so that delayed failures and recurrences may be considered to be extremely rare.

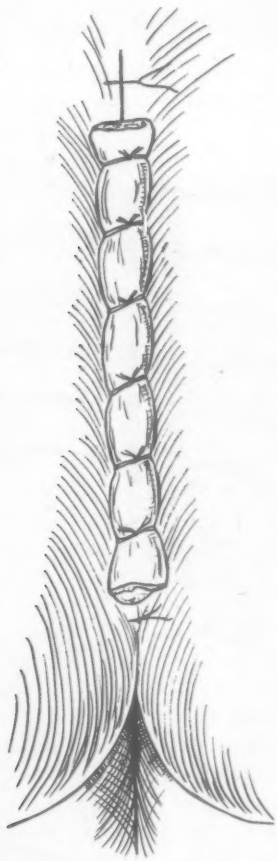

FIGURE 6. *MacFee[2] Type of Partial Closure.*
The wound is frosted with sulfanilamide powder, and the ends of the sutures are tied over a roll of iodoform gauze. This is covered with a pyramidal dressing of gauze. The iodoform roll and sutures are left in place for about ten days.

Grade 3 cysts should not be closed primarily, since this study shows a 53 per cent failure in cases so treated. Some form of partial closure, such as the MacFee operation, is recommended, inasmuch as the period of hospitalization is shorter, the local condition of the scar is better and the possibility of success is greater with partial closure than with the excision and open-packing operation. Since it has become the policy of our services to close primarily only Grade 1 and Grade 2 cysts and to close partially all Grade 3 cysts, the average time of hospitalization has continued to fall.

It is recommended that the frankly septic cases be prepared preoperatively by hot sitz baths and local packs. Preoperative sulfonamides may be used by mouth, sulfanilamide may be dusted in locally at operation, and sulfadiazine may be given by mouth postoperatively.

To become proficient in preoperative grading, the surgeon should check his clinical grading of cysts with the report of the pathologist on the sectioned specimen. In addition, a careful history and physical examination are essential for proper grading; of these, the latter is the more important.

In this series of 128 cases that were operated on, the average hospital stay for all grades from date of operation to complete healing and return to duty was thirty-five days.

On this service the greatest problem in the care of pilonidal cystectomy applies to the excised cyst that has been left open and that heals with resulting excess scar formation. This scar mass tends to break down following trauma and superficial infection, resulting in shallow ulcers that are surrounded by dense fibrous tissue and are slow to heal. The plan adopted in such cases is bed rest, warm antiseptic packs and rigid aseptic technic in handling the dressing until healing is complete. The patient is then educated in the hygienic care and protection of the area before he is sent back to duty.

SUMMARY

It has been the purpose of this analysis to call attention to a method of preoperative grading of pilonidal cysts that has been helpful in determining those cases in which primary closure can be accomplished with a reasonable degree of success. No attempt has been made to bring forward any new type of operation, and all cases were treated by methods that up to this time have been accepted as being surgically sound.

REFERENCES

1. Ferguson, L. K., and Mecray, P. M. Pilonidal cysts: excision and primary suture in ambulatory patients. *Am. J. Surg.* **36**:270-278, 1937.
2. MacFee, W. F. Pilonidal cysts and sinuses: method of wound closure and review of 230 cases. *Ann. Surg.* **116**:687-699, 1942.

THE USE OF GAUZE INOCULATED WITH *PENICILLIUM NOTATUM* OR IMPREGNATED WITH CRUDE PENICILLIN IN THE TREATMENT OF SURFACE INFECTIONS*

R. S. Myers, M.D.,† R. H. Aldrich, M.D., R. W. Howard, M.D.,‡ and R. A. Walsh, B.S.§

BOSTON

RECENT reports indicate that topically applied penicillin solutions and creams are effective in controlling surface infections.[1] There have also been articles suggesting that gauze dressings inoculated with *Penicillium notatum* or impregnated with the crude penicillin have a similar effect. Robinson and Wallace[2] have described a method by which they believe that mold-inoculated dressings can be readily prepared by the physician. They noted subsidence of infection and relief from pain in patients with staphylococcal infections treated by this type of dressing. Hobson and Galloway[3] report 10 cases (burns, lacerations, ulcers and infected sloughing wounds) in which gauze dressings moistened with the crude penicillin produced by *P. notatum* cultures were used. They prevented infection in 3 cases and helped to subdue and control it in 7. Fisher[4] obtained encouraging results from using crude penicillin locally, but noted that it had distinct limitations. He believes that to be effective the dressings should be applied every two or three hours, that crude penicillin, like purified penicillin, is ineffective against certain organisms, and that it is less effective against long-standing infections than against those of brief duration. He noted no toxic effects when the crude penicillin was used either locally or parenterally.

The present clinical study was undertaken to evaluate the use of *P. notatum*-inoculated gauze dressings made according to the method described by Robinson and Wallace. Some of the cases were subsequently treated with dressings impregnated with crude penicillin. Bacteriologic studies were made to determine the bacteriostatic and bactericidal effects of each lot of mold or liquor.

Preparation of Gauze and of Crude Penicillin

Pieces of 28-by-24-mesh absorbent gauze were folded to form eight thicknesses, cut circularly, placed in clean Petri dishes and sterilized in a hot-air oven for one hour at a temperature of 400°F. Five hundred cubic centimeters of distilled water was next placed in an Erlenmeyer flask, to which was added 6 gm. of dehydrated yeast and 12 cc. of glycerin. Finally, a separate mixture of 12 gm. of lactose, 12 gm. of cornstarch and 30 cc. of cold distilled water was added. The contents of the flask was stirred well and boiled for twenty minutes over a low flame. The Petri dishes and culture medium were cooled, and about 60 cc. of the medium was poured into each dish. A bit of the stock culture of *P. notatum*¶ was then transferred to the plate with a flamed platinum loop. The dishes were placed in an incubator at a temperature of 23°C. The penicillin secreted during the growth process was deposited on the under-

FIGURE 1. *The* Penicillium notatum *Growing in an Erlenmeyer Flask.*

The penicillin is secreted on the underside of the mold.

*From the Surgical Service, Peter Bent Brigham Hospital; the Laboratory for Surgical Research, Harvard Medical School; and the Pharmacology and Biology Department, Massachusetts College of Pharmacy.

This study was made possible by a grant from E. L. Patch Company, Boston.

†Instructor in surgery, Harvard Medical School; associate in surgery, Peter Bent Brigham Hospital.

‡Assistant in surgery, Harvard Medical School; junior associate in surgery, Peter Bent Brigham Hospital.

§Instructor in biology and pharmacology, Massachusetts College of Pharmacy.

¶The stock culture was obtained through the courtesy of Charles Pfizer and Company, Brooklyn, New York. It was grown on Sabouraud's dextrose agar, and transfers were made at ten-day intervals to maintain a prolific strain.

surface of the gauze. Its concentration reached a maximum in twelve days and then rapidly retrogressed.

The medium used for the production of crude penicillin was a combination of 96 per cent nutrient broth and 4 per cent corn-steep liquor.* This was placed in flasks, which were sterilized by autoclaving, inoculated with *P. notatum* and incubated for about seven days at 23°C. The liquor, which was partially purified by filtration through a Seitz filter, yielded a high titer of penicillin when assayed by the Oxford method.

The plates containing the impregnated gauze maintained their potency for about two weeks when kept at a temperature of 5°C. or lower, and the crude penicillin liquor could be kept for about four weeks at a temperature of 5°C. without any appreciable loss in titer.

All cultures were examined microscopically for bacterial contamination, and when necessary, subcultures were made. Contaminated plates and flasks were discarded.

*Corn-steep liquor is a by-product in the corn-refining industry and is obtainable from the Corn Products Sales Company, New York, New York.

Method of Applying Dressings

Before the dressings were applied the lesions were prepared by cleansing with an aqueous cationic detergent or with hydrogen peroxide. Gauze pads inoculated with mold or impregnated with crude penicillin liquor were then applied and held in place by adhesive tape or bandage. Several cases of uterine cervicitis were also treated. In these, a pad of the mold-inoculated gauze or of gauze impregnated with crude penicillin was applied directly to the cervix. The dressing was held in place by a vaginal tampon for a period of thirty-six hours. Except for those on the uterine cervix, the dressings were renewed at intervals varying from one to four days. All the patients were ambulatory, thus making it difficult to change the dressings more frequently.

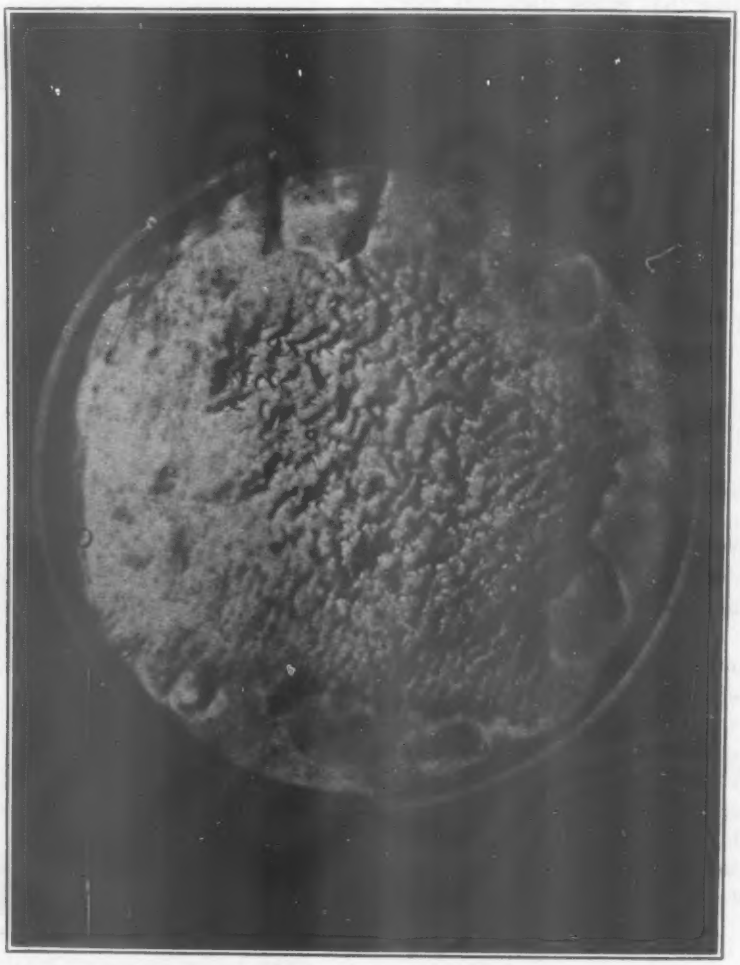

FIGURE 2. *Gauze Inoculated with* Penicillium Notatum *in a Petri Dish.*

Types of Lesions Treated

Thirty-three patients with ulcers of the lower leg or ankle of one week to twenty years' duration were

treated for periods varying from two weeks to three and a half months. There were also 5 patients with chronic uterine cervicitis, 2 with postoperative pilonidal-sinus wounds, 2 with breast wounds following radical mastectomy, in which there was necrosis of the skin and subsequent secondary infection, 2 with draining carbuncles, 1 with a small burn of the neck and secondary infection, 1 with a sloughing perineal wound and 1 with ulcerative stomatitis and secondary infection.

About half the cases were studied bacteriologically. Cultures were made before starting penicillin therapy and repeated during treatment. Most of them showed two or more types of organisms. Twenty-five cases exhibited *Staphylococcus aureus*, 11, *Staph. albus*, 5, beta-hemolytic streptococci, and 4, *Escherichia coli*. A few lesions showed *Proteus vulgaris*, *Bacillus subtilis* and diphtheroid bacilli. After treatment most of the affected surfaces continued to show the same organisms, but in fewer numbers.

In the majority of the cases previous treatment had been employed. Sulfonamide ointments, cationic germicidal solutions, chlorinated solutions and boric-acid ointment were among the substances used without noticeable beneficial effect.

Results

The results of treatment with *P. notatum*-inoculated gauze and crude-penicillin dressings are shown in Table 1.

Comment

The use of gauze inoculated with *P. notatum* or impregnated with crude penicillin was studied in 47 cases of surface infection. In view of the shortage of purified penicillin available for the treatment of surface infections, it was considered worth while to see whether such dressings could be conveniently prepared by the practicing physician. In our experience, homemade penicillin is much more difficult to prepare than is generally appreciated. Civilian physicians are advised to await a more plentiful supply of purified penicillin for the topical treatment of surface infections. Penicillin is too fickle a substance to be prepared by any except experienced hands. The parent mold is difficult to control, and a painstaking bacteriologic technic is required to avoid contamination.

FIGURE 3. *Application of a Mold-Inoculated Gauze Dressing.*

Most of the cases treated in this series were mixed infections, showing more than one type of organism on culturing. The cases that had a pure culture of penicillin-sensitive organisms responded by healing. The cases that failed to heal continued to show the presence of the original infecting organisms, especially *E. coli*, *P. vulgaris* and *Staph. aureus* (a nonsusceptible strain).

Chronic or mixed infections did not respond so well as did acute infections. In the group of 33 patients with chronic ulcers of the lower extremities, many factors other than infection prevented healing. In this group, a different form of therapy intensively followed would probably have given equally good results.

The 13 cases listed as improved, although not entirely freed from the infecting bacteria, were noticeably better in that the wounds looked less angry, were drier and did not have the offensive odor that was usually present before treatment.

No local or systemic toxic effects were noted in any of the patients treated by these methods. There was no evidence of sensitivity, and the patients reported the dressings to be comfortable.

Chronic or mixed infections did not respond so well as did acute infections or those infected with but one strain of a penicillin-sensitive organism.

Because of the difficulties associated with preparing crude penicillin and mold-inoculated gauze, physicians are advised to employ only purified penicillin for the treatment of cases of surface infection.

TABLE 1. *Results of Treatment.*

TYPE OF CASE	NO. OF CASES	RESULT				
		HEALED	IMPROVED	NO CHANGE	WORSE	NO FOLLOW-UP
Leg ulcer	33	14	10	6	1	2
Chronic endocervicitis	5	4	1	–	–	–
Pilonidal-sinus wound	2	1	1	–	–	–
Mastectomy wound	2	2	–	–	–	–
Carbuncle	2	2	–	–	–	–
Burn of neck	1	1	–	–	–	–
Peroneal wound	1	–	1	–	–	–
Ulcerative stomatitis	1	1	–	–	–	–
Totals	47	25	13	6	1	2

SUMMARY

Forty-seven cases of surface infection were treated with *Penicillium notatum*-inoculated gauze dressings and crude penicillin. Twenty-five cases healed and 13 improved during treatment.

REFERENCES

1. Christie, R. V., and Garrod, L. P. Review of work of penicillin therapeutic research unit. *Brit. M. J.* 1:513, 1944.
2. Robinson, G. H., and Wallace, J. E. Inoculated penicillin dressing. *Science* 98:329, 1943.
3. Hobson, A. J., and Galloway, L. D. Home-made penicillin. *Lancet* 1:230, 1944.
4. Fisher, A. M. Antibacterial properties of crude penicillin. *Bull. Johns Hopkins Hosp.* 73:343-378, 1943.

MEDICAL PROGRESS

ENDOCRINE ASPECTS OF CANCER*

IRA T. NATHANSON, M.D.†

BOSTON

THE earliest investigations concerning the relation of hormones to the genesis of tumors relied on indirect evidence. It was not until the isolation and identification of the action of certain of the sex hormones that the problem could be pursued on a more direct basis. Moreover, several of the synthetic carcinogenic hydrocarbons were found to have a basic chemical structure similar to cholesterol and to the hormones of the gonads and adrenal glands. Thus, experimental and clinical studies were further stimulated by the idea that atypical metabolism of the hormones might lead to oncogenesis. As a result of these observations, much information has been accumulated on the role of hormones in carcinogenesis. A symposium on the endocrinology of neoplastic disease was published in the July and August, 1944, issues of *Surgery*. The writer has drawn on these excellent articles, as well as on other leading reviews, as one source of material. The present report summarizes and evaluates, so far as possible, some of the more significant experimental and clinical aspects of the relation of the hormones to carcinogenesis.

*From the Medical Laboratories of the Collis P. Huntington Memorial Hospital, Harvard University, the Tumor Clinic of the Massachusetts General Hospital and the Pondville Hospital, Walpole, Massachusetts (Massachusetts Department of Public Health).

This is publication No. 598 of the Harvard Cancer Commission, Harvard University, and No. 106 of the Pondville Hospital.

†Instructor in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital; assistant surgeon, Pondville Hospital.

EXPERIMENTAL OBSERVATIONS

It is considered important in this review to cite the pertinent animal experiments so that they may be correlated, if possible, with clinical observations. Animals lend themselves readily to studies on cancer, since many develop spontaneous tumors that are similar to those in the human being. Therefore, the subject is reviewed from this standpoint, but it is necessary to stress that caution in interpretation is essential.

Tumors of Breast

Cancer of breast. The early observations of Tyzzer,[1] Slye[2] and others established the role of heredity in the development of tumors in mice. Later studies revealed that other factors were also involved.[3] Thus, it was demonstrated that ovari-

ectomy caused a marked reduction in the incidence of spontaneous mammary cancer[4] and delayed the appearance of those tumors which arose in female mice having a high susceptibility to the disease.[5,6] The reduction in rate varied directly with the age of the mouse at castration, except in newborn mice; for example, the younger the age at ovariectomy, the lower the incidence of tumor. The incidence of breast tumors in mice spayed immediately after birth was higher than in mice castrated at maturity.[7] It has been postulated that after castration in newborn mice the adrenal glands, which secrete steroid hormones, substitute for the ovaries, since mammary and uterine stimulation were noted and adrenocortical hyperplasia developed later in life.[8] Mammary cancer was produced in the male mice of a highly susceptible strain by the transplantation of the ovaries of their sisters,[9] and it was further noted that the incidence of tumors in the female could be reduced by the implantation of testes.[10] Ordinarily, male mice do not develop cancer of the breast. It was also observed that the breast cancer rate was lower in virgin than in breeding females.[10] Forced breeding increased the incidence of breast tumors over that of normally breeding mice.[11] Claims that abnormalities in the sexual cycle are a factor have not been proved.[12] All these experiments suggested the importance of the ovary in the production of such lesions.

After the identification of the estrogens, attempts to produce breast cancer with these hormones were not successful until 1932. Lacassagne[13] was the first to report the appearance of breast cancer after the injection of estrogens in male mice of a strain in which the incidence was high in the female. It was not possible to initiate the disease in males belonging to a strain in which the incidence of mammary tumor was extremely low.[14] Many others have since confirmed and extended these studies.[12,15–17] The administration of estrogens of different chemical structure[14] and synthetic estrogenic preparations, such as diethylstilbestrol[18,19] and triphenylethylene,[20] which are not directly related to the natural compounds or hydrocarbon carcinogenic agents, produced the same effect. Thus, it appears that any compound with the same physiologic effect can elicit the disease and that it is not dependent on a specific chemical structure of the hormone.[21]

Recently, Bittner[22,23] discovered that a third factor, present in the milk of high-tumor-strain mothers, was essential to the development of mammary cancer. The suckling of newborn females of a low tumor strain on high-tumor-strain mothers significantly increased the incidence of cancer of the breast. A reduction in rate was noted if the situation was reversed. Twombly[24] utilized this foster nursing technic and found that it was possible to initiate mammary cancer in male mice of a low tumor strain when they were injected with estrogens. It has been maintained that the extent of response of breast tissue of nonsusceptible animals to estrogens is limited regardless of the duration or the amount of hormone administered. Factors that ordinarily govern cell growth may prevent further progression of cells to a malignant state. Defects in the governing mechanism may allow for neoplastic change, provided the cells are susceptible. Geschickter's[25,26] reports are at variance with this point of view. Rats ordinarily have a low incidence of mammary cancer. He noted a high incidence of mammary cancer in the rat induced by the prolonged administration of estrogens to apparently nonsusceptible animals. Metastases were also observed. Noble, McEuen and Collip,[27] using essentially the same method in a different strain of rats, noted tumors that were extremely hyperplastic. The tumors were not considered to be malignant, even though they resembled the lesions described by Geschickter. Moreover, regressions occurred after removal of the hormonal stimulus.[28] If it is confirmed that mammary cancer can be produced in a species with a nontumor genetic constitution, the role of estrogens as etiologic factors may assume greater significance.

The incidence of breast cancer in mice can be increased by the transplantation of the anterior lobe of the hypophysis under conditions that make possible the long survival of the transplant. Loeb and Kirtz[16,29] found that transplantation of the glands from several brothers to a sister in a high tumor strain appreciably raised the incidence of mammary cancer. This did not occur in the strains in which the susceptibility to tumor was slight. Moreover, cancer could not be induced in the female of the high tumor strain in the absence of the ovaries. Therefore, the increased incidence of cancer was presumably brought about by an increased estrogen production resulting from pituitary stimulation of the ovaries in the intact animal.

Attempts have been made to influence the incidence and course of spontaneous mammary cancer in mice by the administration of gonadotropins. Chorionic gonadotropins had no effect, regardless of the age of the animals at the onset of the experiment, even though there was pronounced enlargement of the ovaries.[30] Equine gonadotropin (pregnant mare's serum) and pituitary gonadotropin retarded the onset and decreased the incidence of the cancer in the virgin mouse when treatment was commenced at approximately one month of life.[31] Administration of the same hormones commencing when the mice were seven months old (the early cancer age) increased ovarian size but did not appreciably alter the onset and course of the tumors.[32] The decrease in incidence produced by these hormones in the young immature animal may be related to the formation of antihormones, which in time would result in ovarian and mammary atrophy.

Thyrotropic extracts have been reported to have an inhibitory effect on the development of mammary cancer,[33] but this has not been confirmed.[34] Hypophysectomy at an early age theoretically reduces the incidence of spontaneous mammary tumors in mice if the animal can be maintained. Gardner,[35] however, found that if mice bearing spontaneous tumors were hypophysectomized in the last half of pregnancy or post partum the tumors grew progressively and new tumors frequently appeared.

Nathanson and Andervont[36] and others[12,37,38] have found that testosterone will significantly lower the incidence of spontaneous mammary cancer in a highly susceptible strain. This is presumably brought about by an antagonism to the estrogens or the inhibition of the pituitary gland, which results in ovarian atrophy, or both. Desoxycorticosterone acetate[39] and progesterone[40] have no influence on the incidence or course of spontaneous breast cancer. None of the hormones tested thus far[12,36] or hypophysectomy[35] has any effect on the course of a tumor once it has developed. No significant difference in the excretion levels of estrogens and 17-ketosteroids has been found between strains with high and low rates of spontaneous mammary tumor.[41]

It is now agreed by most observers that at least three factors are necessary for the genesis of breast cancer in the mouse. These are a heredity factor, the presence of the ovaries or their secretion and the milk influence. All three must be present or cancer does not develop in the experimental animal.[23]

Fibroadenomas of breast. Spontaneous mammary cancer in the rat is infrequent, but fibroadenoma is a relatively frequent disease. One strain, with a relatively high incidence of the tumors, exhibited prolongation of the estrous cycle and a deficiency in ovulation.[42] The initiation of fibroadenomas was attributed to the unopposed action of the estrogens resulting from abnormalities in the sexual cycle. It has been reported that estrogens given over a long period of time produce a high percentage of true fibroadenomas in a strain of rats that ordinarily have a low spontaneous incidence.[26] Others have been unable to confirm this, but the technics were not identical.[43] Studies relative to hormonal influences on the histologic appearance of the tumors are more conclusive. Estrogens stimulate the epithelial elements of early spontaneous, autotransplanted or homotransplanted fibroadenomas and produce adenomas and cystadenomas.[44] Androgens[44,45] and progesterone,[46] on the other hand, inhibit the epithelial component and produce fibrosis. Prolonged administration of estrogens revealed foci of abnormal proliferation of the epithelium in the tumors, which in some cases resembled cancer.[47] Thus it can be seen that in contrast to true cancer, the course and histologic appearance of benign tumors can be altered by hormones.

Tumors of Uterus

Cancer of cervix. Overholser and Allen[48] in 1933, reported the production of a lesion in the cervix in the monkey following estrogen injection that they believed to be carcinoma. Later studies by them[49] and by others[50,51] revealed that the lesion was actually squamous metaplasia. This type of lesion was shown to regress after such a stimulus was removed or when progestin was given with the estrogen.[51] Nevertheless, in 1936 several investigators described the appearance of a carcinoma-like lesion in the cervix of the mouse after estrogen was administered.[52,53] This was of great interest, since cervical cancer does not develop spontaneously in the mouse. Subsequently, the production of cancer of the cervix and vagina after estrogen administration in the mouse has intensively been studied.[12,54–56] The lesions are of the squamous-cell type since the mouse has no mucous glands in the cervix.[57] Early experiments were done in mice that were susceptible to mammary cancer. These studies were complicated by the fact that breast lesions developed before cervical lesions. It was therefore essential to remove the breast cancers as they arose.[54] This pitfall was overcome when it was noted that estrogens could induce cancer in strains of mice that were resistant to mammary cancer.[57] Hence, in contrast to the strain specificity necessary in the development of cancer of the breast in the mouse, the neoplastic response of the cervix to estrogens was not particularly governed by this characteristic. Consequently, there was scant evidence to prove a hereditary influence. Simultaneous administration of androgens or of progestin to any strain of mice did not alter the incidence of cervical cancer.[57] It was also established that the milk influence was not necessary.[57] Since there might be considerable doubt regarding the histologic diagnosis of cancer, several investigators proved the autonomy of the lesion by successful transplantation into other animals of the same strain.[54]

Cancer and hyperplasia of endometrium. Estrogens can produce typical hyperplasia of the endometrium in animals.[58] If treatment is commenced before puberty or is prolonged, squamous metaplasia of the epithelium of the endometrium may occur.[59] Estrogens frequently produce pyometra,[15,60] and some believe that this is the cause of the hyperplasia.[61] Cystic hyperplasia in rabbits,[62] guinea pigs[63] and monkeys[64] similar to that seen in the human female has been observed following prolonged treatment with estrogens. Hypophysectomy increases the susceptibility to the production of endometrial metaplasia not only with estrogens but also with androgens and progestin.[65] Hyperplasia and atypical proliferation of the endometrium follows partial ovariectomy in the guinea pig.[66] Irradiation of the ovaries in the guinea pig[67] and implantation of testicular tissue in mice[68] also result in endometrial

hyperplasia. A protective action of the corpus luteum is suggested by the fact that hyperplasia is less easily induced in the experimental animal by the injection of estrogens if the ovaries are not removed[69] or if progesterone is given simultaneously.[70]

In contrast to cancer of the breast and the cervix, experimental production of cancer of the endometrium is rare. This is of interest because the endometrium is usually susceptible to estrogen stimulation. Greene[71] found that spontaneous tumors develop in the rabbit's endometrium. The lesions, which were said to be adenomas, arose in the glandular mucosa of relatively old animals and spread by local extension and metastasis. Changes similar to those caused by estrogens were found in other organs. These adenomas occurred frequently in animals that had toxemia of pregnancy, which may have produced liver damage and hence an inability to inactivate the estrogens.

Fibromyomas. Numerous attempts to induce fibromyomas of the uterus in species such as mice, rats and rabbits have been without success. The guinea pig is singularly susceptible so that these tumors may be induced simply by the injection of estrogenic hormones.[72–74] The tumors arise usually in the subserosa and the myometrium but sometimes involve the mucosa, thus causing hemorrhage. They may appear throughout the abdominal cavity in both sexes.[73,75] Many are subperitoneal, and although the site of origin is not definitely established, the earliest lesions are found in the peritoneal mesothelium[76] or celomic endothelium.[77] They tend to occur in relation to the mesenteries of the stomach and spleen. Some of the lesions are considered to be malignant since they involve adjacent structures, such as the pancreas, liver and abdominal wall. The lesions are not autonomous because regression occurs when treatment is discontinued.[12,57] Transplantation to another animal is unsuccessful unless the host is injected with estrogens.[57] If progesterone or testosterone[78] or desoxycorticosterone acetate[79] is injected simultaneously with the estrogens, the tumors fail to appear. The initiation of fibromyomas in the guinea pig is therefore a good example of a species susceptibility to tumor formation.

Tumors of Pituitary Gland

Spontaneous tumors of the hypophysis seldom occur in mice or rats. In 1936, three groups of investigators[80–82] reported hypertrophy of the pituitary gland and the formation of chromophobe adenomas in mice and rats of both sexes after continued treatment with estrogens. These adenomas may be transplanted to other animals of the same strain, particularly when the host is treated with estrogen.[12] Pigmented adenomas of the intermediate lobe of the pituitary gland in rats have also been observed after estrogen therapy.[83] These various changes do not occur in all strains of the same species, which demonstrates again the importance of a specific susceptibility to tumor formation. A more detailed review of the subject was recently written by Selye.[84]

Tumors of Testis

Teratomas of the testes of the fowl have appeared after the injection of zinc chloride.[85] In most cases the tumors arose in the spring when spermatogenesis begins, but tumors have likewise been produced in the summer when extracts of the anterior pituitary gland of sheep were injected in combination with zinc chloride.[86] It has been postulated that the tumors arise from the primary germ cells as a result of stimulation of the gonocytes by gonadotropic hormones.[87] Seminomas have appeared after partial gonadectomy,[88] in which case, as the gland regenerated, the spermatogonia went on to tumor formation instead of undergoing normal differentiation. This effect was ascribed to excessive secretion of the gonadotropic hormones as a result of the partial castration, a state that may also arise after necrosis produced by zinc chloride injections. Although the evidence is not conclusive for a hormonal origin, there appears to be a common denominator. All three methods of tumor production, apparently, are related to increased stimulation of the gonads by the gonadotropins.

The production of interstitial cell tumors of the testes in certain strains of mice by the injection of estrogens[89–91] suggests a more definite hormonal relation. Simultaneous injection of testosterone at a certain dose level does not prevent the appearance of tumors, but the rate of change is retarded.[92] In the sequence of events leading up to the development of these tumors, progressive phases of atypical cells appear with atrophy of the tubules. This is manifested by the formation of three generations of Leydig cells. Tumors may arise from any one generation or from a combination of two or of all three generations of cells.[92] These tumors appear malignant and metastasize widely, particularly to the lymph nodes.[90] Transplantation to other animals is successful when the host is treated with estrogen.[92] Long-continued injections of equine gonadotropins elicited changes in the testes of certain mice that resembled those seen in the early stages of the tumors developed by estrogens.[93] Thus, as in the case of the fowl tumors, the gonadotropic hormones may be responsible for the changes. Many of the tumors appear to function, since the seminal vesicles and prostate of the animals exhibited an androgen effect.[90] Tumors of this type produced by any form of estrogen appear to be species limited as well as strain limited. Like cancer of the mammary gland and cervix in the mouse, the tumors arise only after prolonged treatment and after the tissue fails to respond in the usual fashion, or has regressed.[12]

Tumors of Adrenal Gland

Tumors of the adrenal gland in mice are exceedingly rare, but a technic devised by Woolley, Fekete and Little[7,8,94] has resulted in the production of many of these lesions. A variety of changes appear in these glands subsequent to castration in both sexes during the first days of life. The development of the different types of lesions depends to a great degree on the strain used. In one strain, slight hyperplasia occurs, whereas in another, all the mice develop adrenal hyperplasia, nodular or diffuse, which is accompanied by feminization of both sexes.[8] Cancer of the breast may occur in these animals, presumably as a result of estrogenic substances secreted by the adrenal glands. All the animals of a third strain develop adrenocortical carcinoma at about one year of age.[95] Early in the development of the process, before true carcinoma appears, there may be an accompanying feminization, but masculinization appears with the onset of carcinoma. The tumors originate in the outer zones of the cortex, and the transitions from hyperplasia to carcinoma and from a feminization to masculinization can be easily followed.[95] Studies of the excretion of estrogenic hormone in the urine of mice with adrenal hyperplasia reveal about six times as much as is found in control animals.[96]

Lymphoid Tumors

Lymphoid tumors and leukemia arise spontaneously in some strains of mice and rats, and in general there is a higher incidence in the male. Injection of estrogens into any strain of mice that has a tendency to develop these lesions results in an increased incidence of the diseases,[97–99] and the incidence can also be raised by treatment with carcinogenic agents or x-ray.[100,101] As in mammary carcinoma, the milk influence seems to be necessary in the genesis of these lesions.[102] The lesions are usually widespread and can be easily transplanted. Murphy and Sturm[103] reported that removal of the adrenal glands greatly increases the susceptibility of rats to a transplanted lymphatic leukemia. They also found that the injection of adrenotropic hormone, adrenocortical extract and desoxycorticosterone acetate effectively reduced the percentage of "takes" of transplanted leukemic tissue.[104] No effect could be demonstrated on the eventual progress of the disease if the transplants were successful. Castration of the male in one strain of mice increased the incidence of the leukemia to that of the untreated female. Ovariectomy in the female in the same strain had no effect on the incidence of leukemia. Injection of testosterone in the ovariectomized female reduced the incidence to that of the untreated males.[105] In another study the incidence of leukemia in the female was reduced after ovariectomy but orchidectomy in the male had no effect.[106] Although there is some difference between these two studies, the age at castration may have been a factor. Heilman and Kendall[107] noted temporary retardation of the growth of transplanted leukemia after the administration of Compound E. After a time, however, the lesions became refractory and resulted in the death of the animals.

Tumors of Prostate Gland

Enlargement of the prostate gland occurs in over 80 per cent of dogs above the age of about ten years.[108] Huggins and his collaborators[109, 110] demonstrated that androgens given to the dog increased prostatic secretion and produced hyperplasia of the epithelial cells. Metaplasia occurred in some animals, and simulated the histologic appearance of cancer. Castration or injection of estrogens caused regression of the metaplasia and inhibited the production of prostatic fluid. Estrogens in themselves produce enlargement of the prostatic gland in the dog, which regresses when treatment is discontinued. On the other hand, estrogens injected over a long period brings about squamous metaplasia of part of the epithelium of the prostate gland of the mouse.[15, 111, 112] A similar change can be effected in the rhesus monkey.[113, 114] These atypical effects do not occur when testosterone or progesterone is injected simultaneously with the estrogens.[115, 116] In rabbits, estrogen injection causes squamous metaplasia of the urethra around the orifice of the seminal vesicle.[108] Estrogens also cause hypertrophy of the seminal vesicles of mice. In no species of animal, however, has carcinoma of the prostate been produced by the administration of either androgen or estrogen. This is of interest in light of the recent observations regarding the relation of these hormones to cancer of the prostate in man. It appears that both hormones act on the prostate gland but in an entirely different fashion.

Other Tumors

Spindle-cell sarcomas have been reported in mice and rats at the site of injection of estrogens in oil.[117] These have also appeared, however, after the injection of other substances other than estrogens that were dissolved in oil.[118] They have not been observed when pellets of estrogens have been implanted.[12] Osteogenic tumors have been reported as occurring in one strain of mice.[119] Both osteomas and osteogenic sarcomas were observed and were frequently multiple.[120] Approximately 75 per cent of the females and 25 per cent of the males developed these lesions on an average of one and a half years of age, the females developing the tumors somewhat earlier than the males.[119] Injections of estrogens increased the incidence in males and decreased the age at which the tumors appeared in both sexes.[121]

Summary

A wide variety of tumors can be produced or altered in the experimental animal, but these are

dependent on the species, the strain and the individual susceptibility of the animal and there always seems to be some limiting factor in the production of tumors in animals in which attempts have been unsuccessful. Consequently, it is difficult to translate these observations to the study of human cancer. They are, however, of great importance as a tool in the study of oncogenesis in general.

(To be concluded)

References

1. Tyzzer, E. E. Study of heredity in relation to development of tumors in mice. *J. M. Research* **17**:199-211, 1907.
2. Slye, M. Incidence and inheritability of spontaneous tumors in mice (second report). *J. M. Research* **25**:281-298, 1914.
3. Little, C. C. Review of progress in study of the genetics of spontaneous tumor incidence. *J. Nat. Cancer Inst.* **1**:727-736, 1941.
4. Lathrop, A. E. C., and Loeb, L. Further investigation on origin of tumors in mice. III. On part played by internal secretion in spontaneous development of tumors. *J. Cancer Research* **1**:1-20, 1916.
5. Loeb, L. Further investigations on origin of tumors in mice. VI. Internal secretion as factor in origin of tumors. *J. M. Research* **40**: 477-496, 1919.
6. Cori, C. F. Influence of ovariectomy on spontaneous occurrence of mammary carcinomas in mice. *J. Exper. Med.* **45**:983-991, 1927.
7. Woolley, G., Fekete, E., and Little, C. C. Mammary tumor development in mice ovariectomized at birth. *Proc. Nat. Acad. Sc.* **25**: 277-279, 1939.
8. *Idem.* Effect of castration in dilute brown strain of mice. *Endocrinology* **28**:341-343, 1941.
9. Murray, W. S. Ovarian secretion and tumor incidence. *J. Cancer Research* **12**:18-25, 1928.
10. *Idem.* Sex hormones and cancer: some effects of interplay of sex hormones upon incidence of mammary cancer in mice. *Am. J. Cancer* **30**:517-526, 1937.
11. Bagg, H. J. Further studies on relation of functional activity to mammary carcinoma in mice. *Am. J. Cancer* **27**:542-550, 1936.
12. Gardner, W. U. Tumors in experimental animals receiving steroid hormones. *Surgery* **16**:8-32, 1944.
13. Lacassagne, A. Apparition de cancers de la mammelle chez la souris mâle, soumise à des injections de folliculine. *Compt. rend. Acad. d. sc.* **195**:630-632, 1932.
14. *Idem.* Relationship of hormones and mammary adenocarcinoma in mouse. *Am. J. Cancer* **37**:414-424, 1939.
15. Gardner, W. U. Estrogens in carcinogenesis. *Arch. Path.* **27**:138-170, 1939.
16. Loeb, L. Significance of hormones in origin of cancer. *J. Nat. Cancer Inst.* **1**:169-195, 1940.
17. Haagensen, C. D., and Randall, H. T. Production of mammary carcinoma in mice by estrogens. *Arch. Path.* **33**:411-422, 1942.
18. Lacassagne, A. Apparition d'adénocarcinomes mammaires chez des souris mâles traitées par une substance oestrogène synthétique. *Compt. rend. Soc. de biol.* **129**:641-643, 1938.
19. Shimkin, M. B., and Grady, H. G. Carcinogenic potency of stilbestrol and estrone in strain C3H mice. *J. Nat. Cancer Inst.* **1**:119-128, 1940.
20. Robson, J. M., and Bonser, G. M. Production of mammary carcinomas in mice of susceptible strain by synthetic oestrogen, triphenylethylene. *Nature* **142**:836, 1938.
21. Burrows, H. Comparison of changes induced by some pure oestrogenic compounds in mammae and testes of mice. *J. Path. & Bact.* **42**:161-168, 1936.
22. Bittner, J. J. Some possible effects of nursing on mammary gland tumor incidence in mice. *Science* **84**:162, 1936.
23. *Idem.* Breast cancer in mice as influenced by nursing. *J. Nat. Cancer Inst.* **1**:155-168, 1940.
24. Twombly, G. H. Breast cancer produced in male mice of C57 (black) strain of Little. *Proc. Soc. Exper. Biol. & Med.* **44**:617, 1940.
25. Geschickter, C. F. Mammary carcinoma in rat with metastasis induced by estrogen. *Science* **89**:35-37, 1939.
26. *Idem.* Estrogenic mammary cancer in rat. *Radiology* **33**:439-449, 1939.
27. Noble, R. L., McEuen, C. S., and Collip, J. B. Mammary tumours produced in rats by action of oestrone tablets. *Canad. M. A. J.* **42**:413-417, 1940.
28. Noble, R. L., and Collip, J. B. Regression of oestrogen induced mammary tumours in female rats following removal of stimulus. *Canad. M. A. J.* **44**:1-5, 1941.
29. Loeb, L., and Kirtz, M. M. Effects of transplants of anterior lobes of hypophysis on growth of mammary gland and on development of mammary gland carcinoma in various strains of mice. *Am. J. Cancer* **36**:56-82, 1939.
30. Bischoff, F., and Long, M. L. Endocrine factors influencing tumor development: effect of Prolan upon Marsh-Buffalo adenocarcinoma. *Endocrinology* **23**:327-329, 1938.
31. Bischoff, F., Long, M. L., Rupp, J. J., and Clarke, G. J. Endocrine factors influencing tumor development: effect of gonadotropins and of theelin upon Marsh-Buffalo adenocarcinoma and lymphosarcoma. *Endocrinology* **28**:769-779, 1941.
32. Bischoff, F., Rupp, J. J., and Clarke, G. J. Endocrine factors influencing tumor development: administration of gonadotropins at early cancer age to Marsh-Buffalo mice. *Endocrinology* **31**: 329-333, 1942.
33. Cramer, W. Prevention of spontaneous mammary cancer in mice by anterior pituitary hormone. *Am. J. Cancer* **40**:431-433, 1940.
34. Haagensen, C. D., Randall, H. T., and Auchincloss, R. Failure of thyrotropic pituitary hormone to prevent spontaneous mammary cancer in mice. *Proc. Soc. Exper. Biol. & Med.* **45**:820-823, 1940.
35. Gardner, W. U. Persistence and growth of spontaneous mammary tumors and hyperplastic nodules in hypophysectomized mice. *Cancer Research* **2**:476-488, 1942.
36. Nathanson, I. T., and Andervont, H. B. Effect of testosterone propionate on development and growth of mammary carcinoma in female mice. *Proc. Soc. Exper. Biol. & Med.* **40**:421, 1939.
37. Jones, E. E. Effect of testosterone propionate on mammary tumors in mice of C3H strain. *Cancer Research* **1**:787-789, 1941.
38. Heiman, J. Effect of testosterone propionate on adrenals and incidence of mammary cancer in RIII strain of mice. *Cancer Research* **4**:31-34, 1944.
39. Shimkin, M. B., and Grady, H. G. Lack of carcinogenic potency of desoxycorticosterone in mice. *J. Nat. Cancer Inst.* **2**:61-63, 1941.
40. Lacassagne, A. Tentatives pour modifier, par la progestérone ou par la testostérone, l'apparition des adénocarcinomes mammaires provoqués par l'oestrone chez la souris. *Compt. rend. Soc. de biol.* **126**:385-387, 1937.
41. Karnofsky, D. A., Nathanson, I. T., and Aub, J. C. Urinary excretion of estrogens, 17-ketosteroids, creatine and creatinine in high and low mammary tumor strains of mice. *Cancer Research* (in press).
42. Wolfe, J. M., Burack, E., and Wright, A. W. Estrous cycle and associated phenomena in strain of rats characterized by high incidence of mammary tumors together with observations on effects of advancing age on these phenomena. *Am. J. Cancer* **38**: 383-398, 1940.
43. Emge, L. A., and Murphy, K. M. Influence of long-continued injections of estrogens on mammary tissue. *Am. J. Obst. & Gynec.* **36**:750-768, 1939.
44. Heiman, J. Effect of androgens and estrogens in spontaneous benign mammary tumors in rat. *Am. J. Cancer* **40**:343-354, 1940.
45. Mohs, F. E. Transformation of rat mammary adenofibroma to fibroma by androgens. *Cancer Research* **1**:151-153, 1941.
46. Heiman, J. Comparative effects of estrogen, testosterone and progesterone on benign mammary tumors of rat. *Cancer Research* **3**: 65-69, 1943.
47. Wright, A. W., and Wolfe, J. M. Effects of prolonged estrogen administration on spontaneous mammary fibroadenomas in Albany strain of rats. *Cancer Research* **2**:732, 1942.
48. Overholser, M. D., and Allen, E. Ovarian hormone and traumatic stimulation of monkey's cervix to condition resembling early cancer. *Proc. Soc. Exper. Biol. & Med.* **30**:1322-1326, 1933.
49. *Idem.* Atypical growth induced in cervical epithelium of monkey by prolonged injections of ovarian hormone combined with chronic trauma. *Surg., Gynec. & Obst.* **60**:129-136, 1935.
50. Engle, E. T., and Smith, P. E. Some uterine effects obtained in female monkeys during continued oestrin administration, with especial reference to cervix uteri. *Anat. Rec.* **61**:471-483, 1935.
51. Hisaw, F. L., and Lendrum, F. C. Squamous metaplasia in cervical glands of monkey following oestrin administration. *Endocrinology* **20**:228, 1936.
52. Loeb, L., Burns, E. L., Suntzeff, V., and Moskop, M. Carcinoma-like proliferations in vagina, cervix and uterus of mouse treated with estrogenic hormones. *Proc. Soc. Exper. Biol. & Med.* **35**: 320-322, 1936.
53. Lacassagne, A. Tumeurs malignes, apparues au cours d'un traitement hormonal combiné chez des souris appartenant à des lignées réfractaires au cancer spontané. *Compt. rend. Soc. de biol.* **121**: 607-609, 1936.
54. Gardner, W. U., Allen, E., Smith, G. M., and Strong, L. C. Carcinoma of cervix of mice receiving estrogens. *J. A. M. A.* **110**: 1182, 1938.
55. Loeb, L., Suntzeff, V., and Burns, E. L. Growth processes induced by estrogenic hormones in uterus of mouse. *Am. J. Cancer* **34**: 413-427, 1938.
56. Allen, E., and Gardner, W. U. Cancer of cervix of uterus in hybrid mice following long-continued administration of estrogen. *Cancer Research* **1**:359-366, 1941.
57. Allen, E. Estrogenic hormones in genesis of tumors and cancers. *Endocrinology* **30**:942-952, 1942.
58. Taylor, H. C., Jr. Endocrine factors in origin of tumors of uterus. *Surgery* **16**:91-107, 1944.
59. Gardner, W. U., Allen, E., and Strong, L. C. Atypical uterine and vaginal changes in mice receiving large amounts of estrogenic hormone. *Anat. Rec.* (Supp.) **64**:17, 1936.
60. Selye, H., Thomson, D. L., and Collip, J. B. Metaplasia of uterine epithelium produced by chronic oestrin administration. *Nature* **135**:65, 1935.
61. Gardner, W. U., and Allen, E. Some effects of estrogens on uterus of mouse. *Endocrinology* **21**:727-730, 1937.
62. Zondek, B. Effect of prolonged application of large doses of follicular hormone on uterus of rabbits. *J. Exper. Med.* **63**:789-794, 1936.
63. Lipschütz, A., Vargas, L., Jr., Jedlicky, A., and Bellolio, P. Minimum quantity of estrogen required to induce atypical epithelial growth of uterine mucosa in guinea-pig. *Am. J. Cancer* **39**:185-198, 1940.
64. Zuckerman, S., and Morse, A. H. Experimental production of excessive endometrial hyperplasia. *Surg., Gynec. & Obst.* **61**: 15-19, 1935.
65. Selye, H., and Clarke, E. Ovarian function in hypophysectomized rats. *Anat. Rec.* **88**:393-402, 1944.
66. Lipschütz, A. Hyperplasie expérimentale de l'endomètre avec prolifération atypique de l'épithèle utérin après des interventions ovariennes. *Gynéc. et obst.* **36**:408-426, 1937.
67. Schmidt, I. G. Changes in the genital tracts of guinea pigs associated with cystic and "interstitial gland" ovaries. *Anat. Rec.* (Supp.) **70**:69, 1938.
68. Payne, F. L. Clinical significance of endometrial hyperplasia. *Am. J. Obst. & Gynec.* **34**:762-779, 1937.

69. Migliavacca, A. Über die Umwandlung des Uterusepithels in syncytiale Struktur unter hormonalen Einflüssen (Beitrag zur Physiopathologie der weiblichen Geschlechtshormone). *Arch. f. Gynäk.* **159**:172-225, 1935.
70. Nelson, W. O. Atypical uterine growths produced by prolonged administration of estrogenic hormones. *Endocrinology* **24**:50-54, 1939.
71. Greene, H. S. N. Uterine adenomata in rabbit. III. Susceptibility as function of constitutional factors. *J. Exper. Med.* **73**:273-292, 1941.
72. Nelson, W. O. Endometrial and myometrial changes, including fibromyomatous nodules, induced in uterus of guinea pig by prolonged administration of oestrogenic hormone. *Anat. Rec.* **68**:99-102, 1937.
73. Lipschütz, A., and Iglesias, R. Multiples tumeurs utérines et extragénitales provoquées par le benzoate d'oestradiol. *Compt. rend. Soc. de biol.* **129**:519-524, 1938.
74. Moricard, R., and Cauchoix, J. Réalisation de volumineux fibromes chez la femelle de cobaye par l'injection de benzoate de dihydrofolliculine. *Compt. rend. Soc. de biol.* **129**:556-558, 1938.
75. Lipschütz, A., Vargas, L., Jr., and Palma, J. Sex difference in conjunctive tumoral reaction of guinea pig towards natural and artificial estrogens. *Cancer Research* **1**:575-579, 1941.
76. Lipschütz, A., and Vargas, L., Jr. Structure and origin of uterine and extragenital fibroids induced experimentally in guinea pig by prolonged administration of estrogens. *Cancer Research* **1**: 236-249, 1941.
77. Lipschütz, A., Vargas, L., Jr., and Iglesias, R. Sur la structure microscopique des tumeurs utérines et abdominales dues à l'action du benzoate d'oestradiol. *Compt. rend. Soc. de biol.* **129**:524-528, 1938.
78. Lipschütz, A., and Vargas, L. Prevention of experimental uterine and extrauterine fibroids by testosterone and progesterone. *Endocrinology* **28**:669-675, 1941.
79. Lipschütz, A., Vera, O., and Gonzalez, S. Relation of antifibromatogenic activity of certain steroids to their molecular structure and to various actions of these hormones. *Cancer Research* **2**: 204-209, 1942.
80. Cramer, W., and Horning, E. S. Experimental production by oestrin of pituitary tumors with hypopituitarism and of mammary cancer. *Lancet* **1**:247-249, 1936.
81. McEuen, C. S., Selye, H., and Collip, J. B. Some effects of prolonged administration of oestrin in rats. *Lancet* **1**:775, 1936.
82. Zondek, B. Tumour of pituitary induced with follicular hormone. *Lancet* **1**:776-778, 1936.
83. McEuen, C. S., Selye, H., and Collip, J. B. Pigmented adenoma of intermediate lobe in rat chronically treated with oestrin. *Proc. Soc. Exper. Biol. & Med.* **40**:241-244, 1939.
84. Selye, H. Experimental investigations concerning role of pituitary in tumorigenesis. *Surgery* **16**:33-46, 1944.
85. Michalowsky, I. Eine experimentelle Erzeugung teratoider Geschwülste der Hoden beim Hahn. *Virchows Arch. f. path. Anat.* **267**:27-62, 1928.
86. Bagg, H. J. Factors involved in the experimental production of teratoma testis in fowl. In *Some Fundamental Aspects of the Cancer Problem.* 248 pp. New York: The Science Press, 1937. Pp. 92-103.
87. Falin, L. I. Experimental teratoma testis in fowl. *Am. J. Cancer* **38**:199-211, 1940.
88. Champy, C., and Lavedan, J. P. Séminomes par régénérations testiculaires chez les oiseaux. *Bull. Assoc. franc. p. l'étude du cancer.* **28**:503-526, 1939.
89. Bonser, G. M., and Robson, J. M. Effects of prolonged oestrogen administration upon male mice of various strains: development of testicular tumours in Strong A strain. *J. Path. & Bact.* **51**: 9-22, 1940.
90. Hooker, C. W., Gardner, W. U., and Pfeiffer, C. A. Testicular tumors in mice receiving estrogens. *J. A. M. A.* **115**:443-445, 1940.
91. Shimkin, M. B., Grady, H. G., and Andervont, H. B. Induction of testicular tumors and other effects of stilbestrol-cholesterol pellets in strain C mice. *J. Nat. Cancer Inst.* **2**:65-80, 1941.
92. Hooker, C. W., and Pfeiffer, C. A. Morphology and development of testicular tumors in mice of A strain receiving estrogens. *Cancer Research* **2**:759-769, 1942.
93. Pfeiffer, C. A., and Hooker, C. W. Testicular changes resembling early stages in development of interstitial cell tumors in mice of A strain after long-continued injections of pregnant mare serum. *Cancer Research* **3**:762-766, 1943.
94. Woolley, G. W., Fekete, E., and Little, C. C. Gonadectomy and adrenal neoplasms. *Science* **97**:291, 1943.
95. Woolley, G. W. Adrenal cortical tumors and their syndromes in mice. *Cancer Research* **2**:732, 1942.
96. Dorfman, R. I., and Gardner, W. U. Metabolism of steroid hormones. Excretion of estrogenic material by ovariectomized mice bearing adrenal tumors. *Endocrinology* **34**:421-423, 1944.
97. Lacassagne, A. Sarcomes lymphoïdes apparus chez des souris longuement traitées par des hormones oestrogènes. *Compt. rend. Soc. de biol.* **126**:193-195, 1937.
98. Gardner, W. U., Kirschbaum, A., and Strong, L. C. Lymphoid tumors in mice receiving estrogens. *Arch. Path.* **29**:1-7, 1940.
99. Gardner, W. U., Dougherty, T. F., and Williams, W. L. Lymphoid tumors in mice receiving steroid hormones. *Cancer Research* **4**: 73-87, 1944.
100. Morton, J. J., and Mider, G. B. Production of lymphomatosis in mice of known genetic constitution. *Science* **87**:327, 1938.
101. Furth, J., and Furth, O. B. Neoplastic diseases produced in mice by general irradiation with x-rays. I. Incidence and types of neoplasms. *Am. J. Cancer* **28**:54-65, 1936.
102. Law, L. W. Foster nursing and growth of transmissible leukemias in mice. *Cancer Research* **2**:108-117, 1942.
103. Murphy, J. B., and Sturm, E. Adrenals and susceptibility to transplanted leukemia of rats. *Science* **98**:568, 1943.
104. *Idem.* Effect of adrenal cortical and pituitary adrenotropic hormones on transplanted leukemia in rats. *Science* **99**:303, 1944.
105. Murphy, J. B. Effect of castration, theelin, and testosterone on incidence of leukemia in Rockefeller Institute strain of mice. *Cancer Research* **4**:622-624, 1944.
106. McEndy, D. P., Boon, M. C., and Furth, J. On role of thymus spleen, and gonads in development of leukemia in high-leukemia stock of mice. *Cancer Research* **4**:377-383, 1944.
107. Heilman, F. R., and Kendall, E. C. Influence of 11-dehydro-17-hydroxycorticosterone (Compound E) on growth of malignant tumor in mouse. *Endocrinology* **34**:416-420, 1944.
108. Moore, R. A. Benign hypertrophy and carcinoma of prostate. *Surgery* **16**:152-167, 1944.
109. Huggins, C., Masina, M. H., Eichelberger, L., and Wharton, J. D. Quantitative studies on prostatic secretion. I. Characteristics of normal secretion; influence of thyroid suprarenal, and testis extirpation and androgen substitution on prostatic output. *J. Exper. Med.* **70**:543-556, 1939.
110. Huggins, C., and Clark, P. J. Quantitative studies of prostatic secretion. II. Effect of castration and of estrogen injection on normal and on hyperplastic prostate glands of dogs. *J. Exper. Med.* **72**: 747-762, 1940.
111. Burrows, H., and Kennaway, N. M. On some effects produced by applying oestrin to skin of mice. *Am. J. Cancer* **20**:48-57, 1934.
112. Lacassagne, A. Métaplasie épidermoide de la prostate provoquée chez la souris, par des injections répétées de fortes doses de folliculine. *Compt. rend. Soc. de biol.* **113**:590-592, 1933.
113. Van Wagenen, G. Effects of oestrin on urogenital tract of male monkey. *Anat. Rec.* **63**:387-404, 1935.
114. Zuckerman, S. Effects of prolonged oestrogenic stimulation on prostate of rhesus monkey. *J. Anat.* **72**:264-276, 1938.
115. Burrows, H. Protective action of progesterone on genital organs of male mice. *Nature* **138**:164, 1936.
116. Rusch, H. P. Reversal of estrin-induced prostatic pathology in mice by use of testosterone. *Endocrinology* **21**:511-515, 1937.
117. Gardner, W. U., Smith, G. M., Strong, L. C., and Allen, E. Development of sarcoma in male mice receiving estrogenic hormones. *Arch. Path.* **21**:504-508, 1936.
118. Burns, E. L., Suntzeff, V., and Loeb, L. Development of sarcomas in mice injected with hormones, or hormone-like substances. *Am. J. Cancer* **32**:534-544, 1938.
119. Pybus, F. C., and Miller, E. W. Sex-difference in incidence of bone tumours in mice. *Am. J. Cancer* **34**:248-251, 1938.
120. *Idem.* Gross pathology of spontaneous bone tumours in mice. *Am. J. Cancer* **40**:47-53, 1940.
121. *Idem.* Bone tumors and oestrone. *Nature* **142**:872, 1938.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30491

PRESENTATION OF CASE

An eighteen-year-old-girl, a student, was admitted to the hospital with diarrhea.

Nine years prior to admission, at the age of nine, the patient first noted mild diarrhea with two to three soft stools a day. This gradually grew worse over a period of years until two and a half years before entry, at which time she had a sudden increase in the diarrhea, with many watery stools daily, which never contained blood. This was associated with anorexia, nausea, vomiting, discomfort in the right upper quadrant, generalized malaise and some fever. These symptoms were presently followed by deep jaundice. She was treated at a local hospital, where a diagnosis of catarrhal jaundice was made. She remained in the hospital several weeks, and the jaundice disappeared. Following this episode she had a partial remission of diarrhea for about a year. One and a half years prior to admission she developed nasal catarrh associated with fever. During this episode the diarrhea became worse and some blood streaking in the stools was noted; there was no jaundice. The diarrhea showed several remissions and exacerbations, with frequent blood streaking. About five months before admission, a small amount of sugar was found in the urine, and a physician placed her on a strict diabetic diet without insulin. No blood sugar determinations were done at that time. She had considerable anorexia and lost about 35 pounds in four months. The diarrhea continued and was associated with marked tenesmus. Two weeks prior to entry a blood sugar was done at another hospital and was found to be 80 mg. per 100 cc. Because of the persistent diarrhea, an ileostomy was recommended. Five days before entrance into this hospital the diarrhea increased, there being fifteen to twenty watery stools daily, with some blood clots. She developed fatigue, lassitude, drowsiness and a craving for salt and water.

The past history was noncontributory. The patient's mother and her grandfather, aunt and uncle on her mother's side all had diabetes mellitus.

*On leave of absence.

Physical examination revealed a pale, emaciated young girl appearing acutely ill and dehydrated. There was marked clubbing of the fingers. The heart appeared slightly enlarged to the left, and there was a soft blowing systolic murmur over the pulmonic area, which disappeared on inspiration. The abdomen was tender, without spasm. A definitely spastic colon was palpable.

The temperature was 101.4°F., the pulse 136, and the respirations 24. The blood pressure was 120 systolic, 55 diastolic.

Examination of the blood showed a red-cell count of 3,550,000, with 10 gm. of hemoglobin. The white-cell count was 8400, with 73 per cent neutrophils, 26 per cent lymphocytes and 1 per cent monocytes. A catheterized urine specimen had a specific gravity of 1.018, with no albumin or sugar; a few white cells were seen in the sediment. The stool was grossly bloody, with clots. The blood sugar was 95 mg. per 100 cc. The serum nonprotein nitrogen was 23 mg. per 100 cc., the chloride 94 milliequiv. per liter, and the protein 4.95 gm. per 100 cc., with an albumin-globulin ratio of 0.93. The prothrombin time was 33 seconds (normal, 18 to 20 seconds). A urine culture was sterile. A blood Hinton test was negative.

Roentgenograms of the chest and abdomen revealed only some increase in lung markings and a diffuse haziness of the abdomen, suggesting an accumulation of fluid.

The patient's temperature ranged between 100 and 102°F. There was apparently some transient jaundice on the first hospital day, but none thereafter. She was given numerous transfusions of whole blood and plasma, together with intravenous saline solution, Amigen and vitamins, as well as sulfadiazine. On the second hospital day, following a plasma infusion, she developed a chill, with a rise in temperature to 103.6°F. and some vomiting. A blood culture taken at the time was negative. On the following day marked ankle edema was noted, together with basal rales. The serum protein at that time was 4.4. gm. per 100 cc., with a chloride of 92 milliequiv. and a sodium of 128.3 milliequiv. per liter. On the seventh hospital day, proctoscopy revealed an extremely friable bleeding mucosa with a granular and edematous appearance but no frank ulceration. This was thought to be compatible with an acute ulcerative colitis. A stool smear showed no cysts, and there were many red and white cells present. The following day an ileostomy was performed, and examination of a small piece of ileum revealed acute and chronic inflammation with ulceration. At the time of operation about a liter of ascitic fluid was removed.

Following the operation, the temperature rose to 104.5°F., and the edema increased, with distended neck veins, a rapid pulse and slow gasping respirations. The heart was found to be enlarged to the left, and there were moist rales at the bases of the

lungs. At that time the serum protein was 4.97 gm. per 100 cc., with an albumin-globulin ratio of 0.8; the chloride was 91.4 milliequiv. per liter, the prothrombin time 44 seconds (normal, 18 to 20 seconds) and the van den Bergh 3.3 mg. direct, and 8.4 mg. indirect.

The patient was given oxygen and digitalized. She was also given 25 per cent albumin intravenously, as well as plasma and whole blood. She was disoriented, was only slightly responsive and developed a high-pitched cry. No reflexes could be obtained in either the upper or lower extremities. The patient rallied somewhat following the intravenous therapy, the edema decreased, and she became more responsive. On the tenth hospital day aspiration of the stomach by a Levine tube revealed dark-brown fluid that gave a ++ guaiac reaction. The following day the patient suddenly became pulseless and expired.

Differential Diagnosis

Dr. Earle M. Chapman: We are presented with a diagnosis of what was wrong with this patient. It says in the abstract that the patient had acute ulcerative colitis. At operation the surgeon removed a bit of ileum, which was said to show acute and chronic inflammation with ulceration. So as a starting point I think that we have to accept the fact that this patient had colitis and ileitis. But the problem is to explain why an eighteen-year-old girl should have had diarrhea for nine years and then die of the diarrhea. I do not believe that she had only ulcerative colitis and ileitis. There must have been a more deep-seated disease to explain this picture. In the analysis of the situation it comes down to a discussion of what causes prolonged diarrhea in young people.

First we have to consider that this might have been gastrogenous in origin. There is no statement concerning the results of a gastric analysis, but I cannot conceive that lack of hydrochloric acid could have explained this situation, although we know that in old people achlorhydria can cause prolonged diarrhea.

In regard to the colon, we are presented with a statement that she had ulcerative colitis, and although I think that this was not true idiopathic ulcerative colitis, we are not favored with reports of x-ray examination of the bowel to see whether ulcerations were present.

I see Dr. Logan Roots, of China, in the audience; he might suggest that this sounds almost like cholera. There are certain symptoms, such as the craving for salt and water, that suggest that diagnosis. I do not believe, however, that the diarrhea was caused by a bacterial infection.

We have, of course, to consider pancreatic disease as a source for diarrhea, and there I think we are getting a little warmer in this case, because we know that there was a disordered pancreas in the family background. If she had a disordered pancreas, what was the type? The laboratory data are of no help to us, because if she had sprue we should have a better description of the stools, which I should expect to be described as foul, grayish and fat-containing; but nothing is said except that the stools were thin and watery and finally contained blood.

Dr. Benjamin Castleman: They were not fatty.

Dr. Chapman: Another disorder of the pancreas that can lead to this picture and give stools of this character is Chiari's disease.[1] He described four conditions in the pancreas that can cause a disturbance of this sort: cystic degeneration; fibrosis; a condition that is rather unusual, phlebitis or thrombosis in the venules in the pancreas; and hemorrhage and necrosis.

I was interested to note that she had clubbing of the fingers. Why should her fingers be clubbed? X-ray films of the chest did not point to pulmonary disease, although it says there was "slight increase of the lung markings." Andersen and his associates[2] have described cystic degeneration of the pancreas associated with bronchiectasis in the lung, and diarrhea was a prominent feature of the disease. Might she have had this syndrome? There is nothing in the evidence to support it, but one certainly has to mention it.

The last condition to consider is disease of the liver. There are facts in the story that point to primary liver disease in this patient. We know that two and a half years before entry she had anorexia, nausea, vomiting and discomfort in the right upper quadrant, which is anatomically the region of the liver. Following this she had what was said to be "catarrhal jaundice" and thereafter went downhill. In addition, sugar appeared in the urine. Liver disease commonly causes a disturbance in glucose metabolism and has been confused with diabetes mellitus. In further support of liver disease is the low total protein and the high prothrombin time. It is too bad that a cephalin flocculation test or some other test of liver dysfunction was not done. This matter of jaundice appearing and going away is quite surprising, but she must have continued to have jaundice because later the van den Bergh test was 3.3 mg. direct and 8.4 mg. indirect.

If this patient did have some kind of liver trouble, what was the type? It certainly was not portal cirrhosis. Did she have biliary cirrhosis? I cannot say. There is no evidence to support that diagnosis. She did not have a palpable spleen or a big liver, but she did have ascites, and when she was given fluids, she even developed edema. The description of death in the last paragraph sounds to me like that of a patient dying in cholemia.

There is one other rare disease that should be mentioned, another Chiari's[3] disease, not in the pancreas but in the liver, — I have been fooled by that once before here,[4] — that is, a thrombophlebitis in the liver venules themselves. It is a most bizarre picture and is usually seen in older people with carcinoma. This was a young girl, so that we do not suspect carcinoma.

In conclusion, I am forced to make one choice. I have mentioned five possibilities in their increasing order of likelihood. I am going to end up with the final choice that this patient had some type of liver disease, probably Chiari's syndrome. Possibly she had a combination of two of his syndromes, not only a thrombophlebitis of the pancreas but also a peculiar type of cirrhosis following thrombophlebitis within the liver venules. It would not surprise me if she also had bronchiectasis.

Dr. Francis D. Moore: The patient entered on the medical service and was seen in consultation by the surgical service. Most of us lacked Dr. Chapman's diagnostic acumen and were not convinced that there was any pre-existing pathologic process. Her general appearance was thoroughly compatible with one of the extremely sick patients with ulcerative colitis. Clubbing of the fingers has been a repeated observation in ulcerative colitis. This girl had less ascites than some patients with ulcerative colitis. When present, it must be due to the fact that the whole colon is involved as a single tubular abscess and the permeability of the capillaries is increased, so that they pour fluid out into the abdomen as well as into the bowel. She had an ileostomy, and it is routine to resect 1 or 2 cm. of ileum, between clamps, and send it to the Pathology Department to determine whether the disease has extended into the ileum, which is a gloomy prognostic sign. This girl did have ulceration there. The story from there on is up to Dr. Castleman.

Clinical Diagnoses

Chronic ulcerative colitis and ileitis.
Cardiovascular collapse.
Operation: ileostomy.

Dr. Chapman's Diagnoses

Ulcerative colitis and ileitis.
Liver disease (? Chiari's syndrome).
Cholemia.
Bronchiectasis?

Anatomical Diagnoses

Ulcerative colitis, involving entire colon and distal ileum.
Acute hemorrhagic hepatitis, superimposed on toxic cirrhosis.
Fatty vacuolization of liver, severe.
Operation: terminal ileostomy.
Splenomegaly.
Hemorrhage from mucosal and serosal membranes.
Ascites.
Pulmonary edema and congestion.
Anasarca.

Pathological Discussion

Dr. Castleman: The autopsy on this girl showed an extremely acute, as well as a chronic, ulcerative colitis involving the entire colon and the lower 75 cm. of the ileum. There were numerous ulcers, both longitudinal and transverse, without any bridging such as one sees in the more chronic stages, but there was a lot of edema in both the mucosa and the wall. Microscopic sections confirmed a nonspecific acute ulcerative process. We looked hard for amebas but could not find any. The appearance was not inconsistent with what we see in other cases of ulcerative colitis, but as Dr. Chapman implied, that was not the whole story, and he rightly cited the liver as one of the sources of her trouble. The liver presented a striking appearance. Although it was normal in size, weighing 1500 gm., it was composed of bright-yellow fatty irregular nodules, each apparently surrounded by a deep red cuff (Fig. 1). At first we thought that this was a characteristic acute and subacute yellow atrophy of the liver and that these yellow areas were areas of regeneration, the rest being areas of frank necrosis. It would be a little unusual, however, for a person with that amount of necrosis — although there was a lot of regeneration — not to have had more jaundice. Most patients with subacute yellow atrophy are severely jaundiced. Microscopically these nodules were areas of regeneration with extreme fatty vacuolization. The nodules were surrounded by fairly dense connective tissue in which there was extensive hemorrhage.

We know that in ulcerative colitis the almost constant finding at autopsy is a marked fatty vacuolization of the liver, and we can explain all these fatty changes within the regenerated liver nodules as having been due to ulcerative colitis. So this is an example of a healed atrophy type of cirrhosis, the acute attack probably having occurred two and a half years before entry, when she was sick for two and a half to three months. At that time a fair amount of liver tissue was destroyed, this being followed by regeneration. She had recently developed an acute hemorrhagic process of the liver that had little effect on the regenerated nodules. It is quite possible, as has been shown by MacNider[5] experimentally, that regenerated liver cells are more resistant to another toxic attack than are normal liver cells. Perhaps the ulcerative colitis was just a manifestation of the liver disease. We have never seen it so severe as this, but some of the cases of epidemic jaundice that are now being seen in the Army have shown marked edema and inflammation of the colon.[6] I should think that it is fair to assume

that the fundamental disease nine years before entry was ulcerative colitis, that two and a half years before entry the patient developed liver disease and that perhaps the toxins derived from the ulcerative colitis produced this further liver damage.

References

1. Chiari, H. Beitrag zur Lehre von der intravitalen Autodigestion des menschlichen Pankreas. *Prag. med. Wchnschr.* **25**:157-159, 1900.
2. Andersen, D. H. Cystic fibrosis of the pancreas, vitamin A deficiency and bronchiectasis. *J. Pediat.* **15**:763-771, 1939.
3. Chiari, H. Erfahrungen über Infarctbildungen in der Leber des Menschen. *Ztschr. f. Heilk.* **19**:475-512, 1898

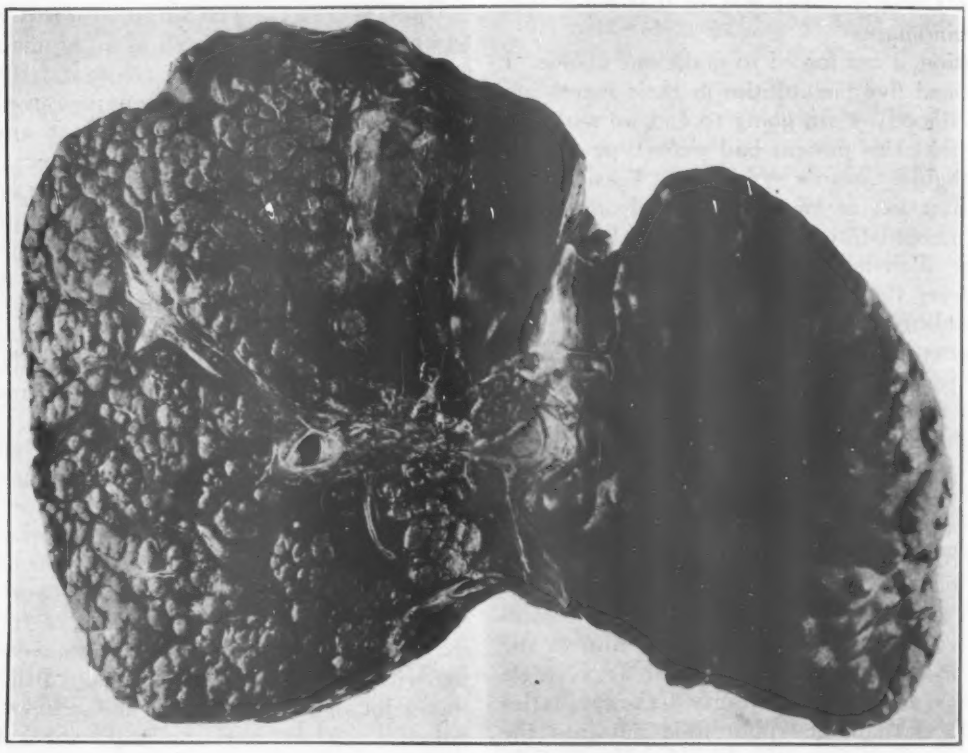

FIGURE 1. *Photograph of Liver.*

DR. FULLER ALBRIGHT: The veins were all right?

DR. CASTLEMAN: It was not Chiari's syndrome.

DR. MOORE: It is interesting that during the same week that this patient died Dr. Altschule and his associates,[7] of the Beth Israel Hospital, reported the cases of 16 or 18 patients who had had catarrhal jaundice at various periods of time up to many years previously. They had subclinical jaundice, as evidenced by an elevated van den Bergh, and it is interesting that of this small group, two had chronic diarrhea and one had frank ulcerative colitis.

DR. CASTLEMAN: I suppose it is possible that the cirrhosis went back more than two and a half years and that the first attack of diarrhea nine years before entry resulted from hepatic disease. I do not know any way of telling, however.

DR. WILLIAM B. BECKMAN: We had a patient with primary liver disease who during the last six or eight weeks of life developed severe ulcerative colitis. We never knew what kind of liver disease it was.

DR. CASTLEMAN: It is striking that Lucké,[6] who worked up the cases of epidemic jaundice for the Army, had a number with involvement of the colon.

4. Case records of the Massachusetts General Hospital (Case 29192). *New Eng. J. Med.* **228**:622-625, 1943.
5. MacNider, W. deB. Study of acquired resistance of fixed tissue cells morphologically altered through processes of repair. IV. Concerning persistence of acquired type of atypical liver cell with observations on resistance of such cells to toxic action of chloroform. *J. Pharmacol. & Exper. Therap.* **59**:393-400, 1937.
6. Lucké, B. I. Pathology of fatal epidemic hepatitis. II. Structure of liver after recovery from epidemic hepatitis. *Am. J. Path.* **20**: 471-593 and 595-619, 1944.
7. Altschule, M. D., and Gilligan, D. R. Chronic latent hepatitis following catarrhal jaundice. *New Eng. J. Med.* **231**:315-317, 1944.

CASE 30492

Presentation of Case

A fifty-one-year-old housewife was admitted to the hospital because of a productive cough.

Six months prior to admission the patient noted a tickling sensation in her throat that caused her to cough and raise sputum. This increased until she was raising about half a cupful of thick green sputum daily, most of it in the morning. During this period she had lost 10 pounds in weight, and noted diminished vigor. Some tenderness was present over the right lower chest. There was no hemoptysis, night sweats, fever or dyspnea.

Two months before entry a roentgenogram of the chest was taken by a physician who recom-

mended a bronchoscopy. This was performed two weeks before admission, and she was told that she had "congestion" in her lungs. She was referred to this hospital for further study.

The patient had had a cholecystectomy twenty years previously. Two months before entrance into the hospital a tumor of the right breast, apparently benign, had been removed.

Physical examination on admission revealed a well-developed, well-nourished woman, not acutely ill. The lower anterior portion of the right chest was tender and dull to percussion, with many moist and crackling rales. A small umbilical hernia was present, and there were marked varicosities of the veins of the lower extremities.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 80 diastolic.

Examination of the urine was essentially negative. A blood Hinton test was negative.

A roentgenogram of the chest revealed an ovoid area of increased density measuring 7 by 4.3 cm., lying across the right lower lung field in the region of the lower lobe (Fig. 1). It was outlined fairly sharply and contained a fluid level. Areas of calcification were present along the lower margin of the mass. The heart and mediastinum were displaced slightly to the right. The remainder of the lung fields was clear. In the lateral view the right lower lobe did not appear to be much reduced in size, but the interlobar septum between the upper and middle lobes was slightly low. A Bucky film revealed the trachea to be normal, and its bifurcation and both main bronchi were well outlined. The lower lobe bronchus could not be followed beyond the mass. An intravenous pyelogram showed prompt dye excretion and normal calyxes, pelves and ureters. There was evidence of considerable pressure on the bladder, particularly on the right, but no definite soft-tissue mass was visible and the organ emptied normally.

FIGURE 1. *Roentgenogram of Chest.*

A bronchoscopy on the second hospital day revealed considerable grayish-white, rather sticky secretion throughout the right bronchial tree. The bronchus of the right lower lobe was reddened and a little edematous, but there was no narrowing. The findings were thought to be consistent with chronic bronchitis.

On the ninth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. LAURENCE L. ROBBINS: I shall not attempt to discuss this case from the clinical standpoint. The roentgenologist is usually asked to examine the patient, make up his mind concerning what the fundamental process is and then use the clinical evidence to arrive at a diagnosis. Consequently let us go at this purely from the roentgenologic approach. Let us look at the intravenous pyelogram

and try to eliminate the urinary tract, because I am going to spend most of the time on the chest findings. So far as I can see, the kidney shadows are normal. There is perhaps a questionable mass in the pelvis, but nothing definite except evidence of pressure on the superior surface of the bladder. So far as the bones are concerned they appear normal for the patient's age, except for some degenerative changes around the lumbosacral joint, and in some films there is a questionable defect in the lateral masses of the fifth lumbar vertebra, which suggests that the patient may have had a spondylolisthesis. I shall discard what goes on in the abdomen. It is going to be embarrassing if the operation on this patient turns out to be abdominal, but I can see nothing from the x-ray standpoint that indicates interference in that part of the body.

The films of the chest show an ovoid lesion. To approach it from an anatomic standpoint, where is this lesion? It appears to be fairly well surrounded by air but extends rather close to the pleura posteriorly. It lies in the right lower lobe, probably in the posterolateral division of this lobe. What are the other features of this mass? It is fairly smooth in outline, contains fluid and air, and in the lower margin of the mass there appear to be flecks of calcification. The wall of the mass is thin, although we do not know whether that is true regarding the entire circumference. Fluoroscopy would be helpful because one could tilt the patient from one side to the other to change the level of fluid and thereby get a better view of the wall.

What else is going on within this lobe? Perhaps it is a little smaller than usual, and I think that the septum between the middle and the lower lobes lies farther posterior than is the usual finding. Also, some of the bronchi are perhaps slightly dilated.

In regard to differential diagnosis, the first question is, Is this a tumor? Yes, it could be a primary tumor that had become necrotic in the center and was draining through a bronchus. One factor against that is the rather thin wall, and where we are able to visualize it, the lesion appears to be fairly smooth in outline. Could it be metastatic tumor from carcinoma or sarcoma elsewhere? Yes, but it is rather rare for metastatic lesions to break down and drain into a bronchus. Could it be a lymphoma? Lymphoma of the lung is relatively rare, and in the few cases that I have seen, it has not broken down; nor have I seen calcification within it. That more or less covers the group of tumors. I cannot completely rule out carcinoma, but it does not seem likely.

Could it be a tuberculoma? It is in the lower lobe, and in the few cases that we have seen the majority of the lesions have been in the upper lobe. The calcification would go with tuberculoma. We shall have to wait and see if we can find anything in the clinical findings that will be of help.

Could it be an abscess? If it were an abscess, I should think that it would be on the basis of inhalation or associated with bronchiectasis. The calcification in the wall could go with long-standing abscess, and the rather thin wall could again go with it, because it would mean that the abscess had been present for a long time, developed a capsule and was well localized. I do not believe that it was an abscess on the basis of a septic infarct because that usually clears in a relatively short time, and in the cases that we have seen they have not localized quite so well as this.

Then we come to the possibility of bronchiogenic cyst, or what is often called a "hamartoma." So far as I can gather, the difference between a true bronchiogenic cyst and a hamartoma is essentially that the cyst contains more glandular material within it and secretes the mucoid material that is so characteristically found in these cysts. It certainly could be a bronchiogenic cyst that had become necrotic and was draining through a bronchus. I do not believe that the calcification within the wall is against such a diagnosis.

I have covered the x-ray examinations fairly thoroughly, and in general my interpretation has not varied greatly from the original one. Now let us turn to the clinical findings to see if we can get any further information. We have the story of a patient raising large amounts of sputum, which is consistent with bronchiectasis or an abscess or a bronchiogenic cyst that had become infected and drained into a bronchus. I still cannot rule out necrotic tumor, but there is no evidence of hemoptysis, which is of considerable importance. A previous x-ray examination for comparison would be a tremendous help. We do not have that by any chance?

DR. BENJAMIN CASTLEMAN: No.

DR. ROBBINS: In the past history we find that the gall bladder and a tumor of the right breast had been removed, which raises the remote possibility of metastatic tumor. But for the reasons that I have given we shall disregard that diagnosis. It is difficult to explain the physical findings entirely by the lesion in the chest. There is, however, a shadow in the anterior costophrenic angle that may or may not be of significance. The number of things that it could be in that area are legion, and I am not going to get mixed up in a discussion of them. So we come down to the fact that this patient had had a six-month story of raising fairly large amounts of sputum in the morning. I cannot take a definite stand and say whether this was due to a lung abscess, tuberculoma or infected bronchiogenic cyst, but I am inclined to put the most emphasis on a long-standing lung abscess, even though the history does not exactly fit in with it, and put as my second choice an infected bronchiogenic cyst.

DR. CASTLEMAN: Are there any further suggestions?

DR. HELEN S. PITTMAN: I should put abscess first on the list. I think that it is surprising, however, if this was an abscess, that the patient had no fever and no elevated white-cell count. There is no description of the sputum. If it were an abscess, one would expect the sputum to be unpleasant enough so that there would have been a note about it somewhere.

DR. RALPH ADAMS: I believe that it was a bronchiogenic cyst, not a chronic lung abscess and not a malignant tumor with central necrosis. It seems to me that a lung abscess of six months' duration would have had a wall that was thicker than the apparently thin wall in this case. Furthermore, the sputum in a lung abscess with the amount of sputum that she had would, almost certainly, have been foul at times and very likely would have been bloody. The lung tumors with central necrosis have, by and large, a so-called "sore thumb" sign. One sees air at the top of the cyst and a suggestion of fluid level, but protruding above the level of the fluid there tends to be a piling up in the center, which has come to be recognized as the tumor seen in profile. In addition, a malignant tumor, particularly if it is breaking down, almost always causes hemoptysis. For these reasons I think that the lesion was a bronchiogenic cyst.

CLINICAL DIAGNOSIS

Bronchiogenic cyst.

DR. ROBBINS'S DIAGNOSIS

Lung abscess?
Bronchiogenic cyst, infected?

ANATOMICAL DIAGNOSES

Lung abscesses.
Bronchiectasis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The patient was operated on, and the right lower lobe was removed. There were no adhesions over the surface of the lobe, and apparently the surgical procedure was not particularly difficult. We were able to feel a hard mass within the lobe, and the surgeon, before removing the lobe and therefore before the surrounding lung had collapsed, reported that the mass was extremely hard; because of this and because he was unable to feel any fluctuation, he toyed with the idea that it was a tumor.

After fixation the lung was sectioned. In the central portion of the lobe we were able to find three cavities, two communicating with each other, but one separate from the others. They all communicated with a major bronchus (Fig. 2). The walls were thin, measuring only 1 mm. in thickness in most places. The inner surfaces of these cavities were granular, and microscopic studies showed no evidence of tuberculosis. All the cavities were lined by bronchial mucosa, and I therefore believe that they were abscesses, perhaps bronchiectatic, rather than bronchiogenic cysts. I do not suppose there is any real way of proving this except that the walls were exactly like that of a bronchus. One did not have to hunt for the various bronchial elements in the wall as one usually does in bronchiogenic cyst. Whether this was a bronchiectasis with abscess formation or whether it started out as an abscess and secondary bronchiectasis developed I do not believe that anyone can say. The fact that there was no involvement of other bronchi is suggestive that it started as an abscess, which later communicated with a bronchus. That there were three of them is also in favor of their being abscesses.

FIGURE 2. *Photograph of Resected Right Lower Lobe.*

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board
Joseph Garland, M.D. A. Warren Stearns, M.D.
Shields Warren, M.D. Dwight O'Hara, M.D.
C. Guy Lane, M.D. Chester S. Keefer, M.D.
William A. Rogers, M.D. Howard M. Clute, M.D.
Stephen Rushmore, M.D. Fletcher H. Colby, M.D.
Henry R. Viets, M.D. Robert L. Goodale, M.D.
Robert M. Green, M.D. Chester M. Jones, M.D.
Charles C. Lund, M.D. Harvey R. Morrison, M.D.

Associate Editors
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.
Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year (Boston funds); $8.52 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

THE CHRISTMAS SEAL CAMPAIGN

The seriousness of the tuberculosis problem is strikingly shown by statistics recently issued by the National Tuberculosis Association. One out of every hundred men examined for military service has been disqualified by having the disease — 30 per cent showing it in a clinically active form. Furthermore, in the thirty-one months after Pearl Harbor the deaths from tuberculosis in the United States were nearly three times those occurring in combat — 145,000 against 57,000.

Although the tuberculosis death rate has been reduced 75 per cent in the last forty years, its ravages continue, in spite of the fact that the means of prevention and cure are well established. Fifty-six thousand people in this country died of tuberculosis last year, and it is estimated that over half a million people have the disease, only half of these being known cases. In the war-torn countries of Europe the problem is, of course, ever so much more serious. In the United States, indications point to a reversal of the downward trend of mortality unless drastic steps are taken to prevent it.

These facts give special importance to the approaching Christmas Seal Campaign. The funds thus raised will be devoted to widely performed x-ray examinations of the chest, to the follow-up and treatment of cases thus discovered and to many kindred activities in the fight against tuberculosis. In buying Christmas Seals to the limit of our resources, we shall not only be aiding in a domestic war but in no small measure be contributing toward the military victory that is sure to come.

THE FAT OF THE LAND

Since the strict rationing of 40 per cent cream went into effect on August 1, a monthly saving of 2,300,000 pounds of butter fat has been effected in the sixteen federal market areas, according to advices from the War Food Administration. In the face of such startlingly good results from a program that has been none too popular, although ostensibly designed to increase the amount of butter available to the consumer, the rise in the point value of the commodity to the almost prohibitive level of twenty points per pound is unfortunate and is hard to explain to the little people who are supposed to constitute the backbone of the nation. The explanation, however, has been made in a recent broadcast of Mr. John H. Sullivan, district director of distribution of the War Food Administration.

The first reason for the current butter shortage according to Mr. Sullivan, is that the current butter production is 17 per cent lower than the 1935-1939 average. A second reason is that we are sharing our supplies with both American and Allied fighting men. A third is that more people can afford to buy butter than ever before, because wartime incomes are higher; and a fourth, that the increased milk output is not going into butter but

into other uses. Civilians, for instance, are drinking from 20 to 25 per cent more milk than formerly, and the armed forces have asked the manufacturers of evaporated and condensed milk for a 75 per cent increase in these products over last year.

Despite a 14 per cent increase in milk production since the years before the war, butter production, as has been indicated, has fallen off 17 per cent. Of the butter manufactured, 80 per cent of the total is available to civilians, 15 per cent is set aside for military purposes, and 5 per cent goes to Russia for use in military hospitals. The average civilian share will be something less than twelve pounds per person this year, as compared with nearly seventeen pounds between the years 1935 and 1939.

It is a poor American, indeed, who will not make enlightened sacrifices to help in winning the war, although he may still wonder why all but two and a half of his weekly red points are required to secure this allotted butter ration. Those of us who have seasoned our patriotism with philosophy, however, will continue cheerfully to do without heavy cream, and will learn that oleomargarine is an excellent substitute for the theoretical twelve pounds of butter.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON POSTWAR PLANNING

The first meeting of the Committee on Postwar Planning, appointed by the President of the Massachusetts Medical Society, was held on November 8 with twenty-three members present. Important topics considered for committee action included the problem of providing both short-term and long-term residencies and refresher courses to medical men returning from service, the place of the hospital in postwar education, opportunities for doctors in public health and the relation of medicine to changing economic conditions.

The Committee begs the interest and co-operation of the members of the Society and asks that questions be sent to the chairman. Information bureaus at the headquarters of the American Medical Association and, for Massachusetts, at 8 Fenway, Boston, are expected to help physicians returning from service.

HOWARD F. ROOT, *Chairman*

DEATHS

BAUMAN — Julia L. Bauman, M.D., of Holyoke, died November 17. She was in her sixty-third year.

Dr. Bauman received her degree from the Women's Medical College of Pennsylvania. She was reputed to be the first woman of Polish birth to practice medicine in Massachusetts.

DRAPER — Frank E. Draper, M.D., of Framingham, died November 24. He was in his eighty-first year.

Dr. Draper received his degree from Harvard Medical School and studied at Vienna University. He was formerly assistant ophthalmic surgeon at the Massachusetts General Hospital and the Boston Dispensary and clinical assistant at the Massachusetts Eye and Ear Infirmary. He was a member of the New England Ophthalmological Society. He served as a captain in the Army Medical Corps during World War I.

His widow, a daughter, a granddaughter and a great granddaughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

USE OF DIPHTHERIA TOXOID IN ADULTS

Diphtheria toxoid is now the universally accepted agent for the immunization of children against diphtheria. It has been extensively used in adolescents and adults as well, but it is prone to cause marked reactions in a certain percentage of these unless small initial doses are used and subsequent doses are adjusted according to the presence or absence of a reaction to the first dose.

Since reactions to diphtheria toxoid in adolescents or adults are most frequent and severest in persons who are immune to diphtheria, it is of course essential that these be excluded from any immunization program by previous Schick testing. By taking this elementary precaution and by starting with a small initial dose (0.1 cc.) as indicated above, it is entirely practical to immunize adolescents or adults with diphtheria toxoid.

The practice of immunizing such persons with diphtheria toxin-antitoxin mixture has been abandoned almost everywhere, since toxin-antitoxin is less efficient than toxoid as an immunizing agent, and also because it necessarily contains serum from a horse or other animal. For these reasons, the use of toxin-antitoxin for individual immunization is no longer recommended, and *the department will discontinue the distribution of the package containing three 1-cc. vials of toxin-antitoxin as of January 1, 1945.*

Since the routine use of diphtheria toxoid in groups in which individual adjustment of the dosage is not practical is not as yet entirely satisfactory, toxin-antitoxin mixture in 20-cc. vials will continue to be furnished.

Interpretation of the Schick test. The usual instructions for interpreting this test state that subjects showing positive reactions with toxin and positive but smaller reactions with the control material are susceptible to diphtheria but are also sen-

sitive to the proteins of the diphtheria bacillus. Such persons are *exceedingly* likely to react either to toxin-antitoxin mixture or to toxoid, and should be immunized cautiously, if at all. Recent experience suggests that many such subjects are actually immune to diphtheria. Whenever there is doubt concerning the best immunizing procedure to follow, it is suggested that the person in charge consult the director of either the Division of Biologic Laboratories or the Division of Communicable Diseases regarding the advisability of determining the patient's serum antitoxin titer. This test which can be done in four or five days, is a valuable method for determining the patient's immunity. It can be carried out with 5 to 10 cc. of blood sent, preferably in a sterile tube, to the Antitoxin and Vaccine Laboratory.

BOOK REVIEW

Medical Clinics on Bone Diseases: A text and atlas. By I. Snapper, M.D. 4°, cloth, 225 pp., with 30 plates and 39 tables. New York: Interscience Publishers, Incorporated, 1943. $10.75.

This monograph will prove stimulating to internists, surgeons, endocrinologists, roentgenologists and orthopedists. The author has had a wide experience in Amsterdam and later as professor of medicine at the Peiping Union Medical College in China, and he draws liberally from it in this critical review of recent concepts of certain of the bone disorders. The text is built around a group of the author's cases, which are given in considerable detail; the dissertation on each disease condition includes a discussion of the history, pathology, clinical symptomatology, biochemistry, pathologic physiology, differential diagnosis, etiology and treatment. A unique feature is the inclusion of photographic prints of the x-ray films, bound as full-page inserts with the text. As a result, the illustrations are decidedly superior to those usually found in reference books. An extensive bibliography is included at the end of each chapter; an author and a subject index are placed at the end of the monograph.

The author devotes half the monograph to a discussion of conditions associated with hyperfunction of the parathyroid glands, both primary and secondary. He discusses, among other topics, von Recklinghausen's observations, classic osteitis fibrosa cystica with gross bone involvement, renal complications of hyperparathyroidism, with and without involvement of the skeleton, gastrointestinal symptoms from hypercalcemia, differential diagnosis of hyperparathyroidism, and various phases of parathyroidectomy. Although the general discussion is excellent, the interpretation given to some of the investigations quoted from the literature are misleading and tend to undermine confidence in the rest of the work. Little discussion is made of the point that bone disease need not develop in patients with hyperparathyroidism if sufficient calcium and phosphorus are ingested in the diet; as a corollary to this, the author is reluctant to admit the existence of cases in which the only demonstrable pathology is in the renal system, although these are commonly found by physicians on the alert for them.

Hyperparathyroidism secondary to osteomalacia and chronic renal insufficiency are discussed. To the reviewer, this chapter seems rather confused. Although in an earlier section the author calls attention to the fact that acidosis induces osteitis fibrosa, he gives little consideration to acidosis as a cause of the bone lesions in the cases with chronic renal insufficiency; furthermore, he does not discuss the effect of correcting the acidosis on the bone lesions or on the abnormal calcium and phosphorus levels in the blood. He notes that some cases have hyperphosphatemia because of phosphate retention and that some cases have hypophosphatemia, which he believes is due to osteomalacia from poor diet and lack of sunlight instead of hyperparathyroidism; he does not discuss the hypocalcemia in these cases as a result of excretion in the urine of calcium as a fixed base to combat the acidosis.

The author gives an interesting account of osteomalacia as it is found in China, where poor diet and lack of exposure to sunlight combine to produce avitaminosis D. In the United States, however, osteomalacia is commonly seen only as a result of steatorrhea from such disorders as nontropical sprue or pancreatic disease; no discussion of these conditions is included. This section would also have profited from some consideration of the effect of vitamin D on calcium and phosphorus metabolism. Excellent chapters are included on Paget's disease of bone, Gaucher's disease and multiple myeloma. The illustrations and the cases in these sections are among the best in the monograph.

A detailed discussion is given of lipoid granulomatosis and xanthomatosis of the bones. The author contends at some length that osteitis fibrosa disseminata (Albright) or multiple fibrous dysplasia (Lichtenstein) is a manifestation of lipoid granulomatosis of the bones, but his evidence is not convincing. He points out that lipoid infiltration is usually a secondary process even in so-called "lipoid granulomatosis"; hence, secondary infiltration with lipoid might reasonably be expected to occur in an occasional case of osteitis fibrosa disseminata. Furthermore, his insistence that lipoid infiltration can be demonstrated only in a biopsy of a fresh lesion is difficult to reconcile with lipoid infiltration as a secondary process; that is, one would not expect to find it in the earliest lesions.

In the differential diagnosis of hyperparathyroidism, the author considers Paget's disease, multiple myeloma, generalized cancer metastases in the bones, decalcification of the bones in hyperthyroidism, lipoid granulomatosis of the bones or xanthomatosis ossium (including osteitis fibrosa disseminata), chronic renal insufficiency and osteomalacia. One is disappointed not to find a discussion of sarcoidosis, lymphoma involving bone, benign metastasizing hemangioma and osteoporosis. One would like also to have found included in this monograph some discussion of neurofibromatosis, osteopetrosis, the effect of lead and fluoride on bones, hypoparathyroidism and the various conditions causing tetany. The most surprising omission is osteoporosis. This condition, which is considered to result because of a defect in the formation of the matrix rather than in the calcification of it, is not clearly defined in the monograph. At times the author appears to be using osteoporosis as a general term for a rarefied bone. Osteoporosis has been found associated with immobilization and reduction in stress and strain, senility, postmenopausal state, Cushing's syndrome, hyperthyroidism and conditions associated with protein depletion (hunger osteopathy). Osteoporosis has been recognized as one of the commonest metabolic bone disorders, — postmenopausal osteoporosis, in particular, having been widely observed. The author barely mentions a few of these conditions. Exception must also be taken to certain statements. The author speaks of normal calcium and phosphorus metabolism when he means normal levels of calcium and phosphorus in the blood; he states that, in bone metastases from cancer of the prostate, acid phosphatase is constantly present when he means that it is usually elevated above the normal level.

In spite of these criticisms, most of which would be passed over by the casual reader, the monograph is a valuable contribution in a field largely unknown to most physicians. It should find considerable use as a reference work among persons interested in these disorders.

The publishers are to be commended on the mechanical features of the book: it has excellent illustrations, good type, substantial paper, sturdy binding and no typographical errors.

NOTICES

NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Harvard Club on Friday, December 15. There will be an x-ray conference at 4:30 p. m. At 8:00 p. m. Dr. Kurt H. Thoma will speak on the subject "Tumors of the Jaw."

(*Notices continued on page xv*)

NOTICES (*Continued from page 780*)

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, December 14

Friday, December 15
*9–10 a.m. The Cushing Syndrome. Dr. Kenneth W. Thompson. Joseph H. Pratt Diagnostic Hospital.
10:50 a.m. Postgraduate clinics in dermatology and syphilis. Dowling Amphitheatre, Boston City Hospital.
8:00 p.m. New England Roentgen Ray Society. Harvard Club, Boston.

Saturday, December 16
*10.00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, December 18
12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, December 19
*12:15–1:15 p. m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
8:15 p. m. Harvard Medical Society. Peter Bent Brigham Hospital.

Wednesday, December 20
*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

December 9. American Federation for Clinical Research. Page xiv, issue of November 9.

December 12. Harvard Medical Society. Page 752, issue of November 30.

December 13, and January 3 to April 25. Metropolitan State Hospital. Page 508, issue of October 5.

December 13. Some Effects of Injected Cytachrome C in Animals and Man. Dr. Samuel Proger. Joseph H. Pratt Diagnostic Hospital.

December 14. Some Aspects of Gastric and Duodenal Pathologic Conditions with Particular Reference to the Correlation of Physician and Surgeon. Dr. L. S. McKittrick. Pentucket Association of Physicians. 8:30 p. m. Haverhill.

January 20 and 21. Forum on Allergy. Page 638, issue of November 2.

February 3. American Board of Obstetrics and Gynecology. Page 696, issue of November 16.

February 19. American Board of Internal Medicine. Page 436, issue of September 21.

May 22–24. Hotel Statler, Boston. Annual meeting of the Massachusetts Medical Society.

September 17. American Public Health Association. Page 752, issue of November 30.

District Medical Societies

PLYMOUTH
January 18. Brockton Hospital, Brockton.
February 15. Jordan Hospital, Plymouth.
March 15. Goddard Hospital, Brockton.
April 26. Toll House, Whitman.
May 17. Lakeville Sanatorium, Lakeville.
All meetings will be held at 11 a. m.

WORCESTER
December 13. Worcester City Hospital.
January 10. St. Vincent Hospital, Worcester.
February 14. Worcester State Hospital.
March 14. Worcester Memorial Hospital.
April 11. Hahnemann Hospital, Worcester.
May 9. Annual meeting.

Harvard Medical School

Courses for Graduates

PATHOLOGY OF OBSTETRICS AND GYNECOLOGY

By Dr. Arthur T. Hertig at the Free Hospital for Women

January 4–June 7, 1945

Thursdays, 9:30 a.m. to 12:30 p.m.

Fee — $125

Apply to Assistant Dean, Courses for Graduates
Harvard Medical School, Boston, Massachusetts

Channing Sanitarium

Established 1879

A pleasant country community of cottages built for the homelike care and treatment of nervous patients. Separate cottage for the care of convalescent nonmental patients. Occupational therapy. Tennis court. Sports building.

Jackson M. Thomas, M.D., *Superintendent* — Clifford G. Rounsefell, M.D., *Resident Physician*

WELLESLEY, MASSACHUSETTS

Telephone — Wellesley 0464

BREAST MILK

may be obtained at the offices and laboratory of

The Directory for Mothers' Milk

Incorporated

221 Longwood Avenue, Boston
Telephone BEA 5330

Prices will be adjusted to make the milk available to all who need it

Sent packed in ice to all parts of New England

Bournewood Hospital

300 SOUTH STREET, BROOKLINE, MASS.

Established 1884

For a limited number of cases of mental and nervous diseases

POST OFFICE, CHESTNUT HILL

Telephone PAR 0300

George H. Torney, M.D.

Washingtonian Hospital

41 WALTHAM STREET, BOSTON, MASS.
Founded 1841
A non-profit-making, endowed institution reorganized, for the
MODERN TREATMENT OF MEN SUFFERING FROM ACUTE OR CHRONIC
ALCOHOLISM

Joseph Thimann, M.D., *Medical Superintendent*
Merrill Moore, M.D., *Director of Research*

Visits by Psychiatric and Neurological Staff Consultants in Medicine, Surgery and the Specialties
Rates Moderate
For information: consult the Medical Superintendent
Telephones: HAN 1750 and 1751

The rooster's legs are straight.

The boy's are not.

The rooster got plenty of vitamin D.

Fortunately, extreme cases of rickets such as the one above illustrated are comparatively rare nowadays, due to the widespread prophylactic use of vitamin D recommended by the medical profession.

One of the surest and easiest means of routinely administering vitamin D (and vitamin A) to children is MEAD'S OLEUM PERCOMORPHUM WITH OTHER FISH-LIVER OILS AND VIOSTEROL. Supplied in 10-cc. and 50-cc. bottles. Also supplied in bottles of 50 and 250 capsules. Council Accepted. All Mead Products Are Council Accepted. Mead Johnson & Company, Evansville 21, Ind., U. S. A.